MAY 1954
VOL. IX NO. 5

Circulation

JOURNAL of the AMERICAN HEART ASSOCIATION

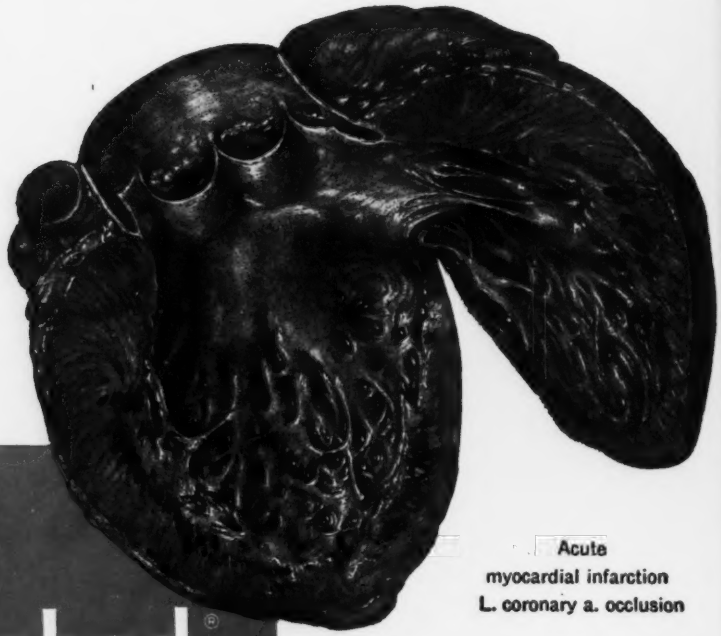
BOSTON UNIVERSITY
COLLEGE OF LIBERAL ARTS
LIBRARY

QP
101
.C5

Published by Grune & Stratton, Inc.

—in the severe shock

secondary to myocardial infarction



Acute
myocardial infarction
L. coronary a. occlusion

WINTHROP

Levophed®

BITARTRATE

..... may be life-saving

A series of 14 cases of severe shock accompanying myocardial infarction was treated by various methods. All of the 6 patients who received Levophed recovered despite the presence of congestive heart failure.[1]

The practically instant pressor effect of Levophed—within 10 to 30 seconds—may usually be maintained at desired levels almost indefinitely.

Write for detailed literature.

Winthrop-Stearns INC.
NEW YORK 18, N. Y. • WINDSOR, ONT.

1. Gazes, P. C., Goldberg, L. I., and Darby, T. D.: *Circulation*, 8: 883, Dec., 1953.

Levophed bitartrate, brand of levarterenol bitartrate

ture.

INC.
ONT.

Circulation
A Journal of the American Heart Association
MAY 1954
VOL. IX NO. 5

Intrinsic Blood Pressure

By ROBERT M. ANDERSON, M.D.

In this paper a concept of intrinsic blood pressure is formulated. This pressure was measured in 84 subjects with normal and abnormal vascular systems. It is concluded that shock, congestive failure, hypertension and the normal vascular system can be defined and understood in terms of intrinsic blood pressure.

STUDENTS of the cardiovascular system in the past have given little thought to the hydraulics of this system as a whole in relation to its outside environment. Instead, they have been concerned with circulation within the system and the resulting hydraulic differences between its parts, described in terms of circulation time, cardiac output, peripheral resistance, arterial pressure, venous pressure and velocity of blood flow.[1-5, 7-10, 12, 13] This study is an investigation of the vascular system as a hydraulic unit in 81 persons.

An attempt was made to measure the pressure in the vascular system as a whole without the alterations in pressure from place to place within it that are caused by circulation. To do this the circulation by the heart must be stopped and the pressure throughout the cardiovascular system allowed to equalize. This must be done without any alteration in the factors responsible for moving fluid into or out of the system. The pressure in the vascular system as a whole will be referred to as the *intrinsic blood pressure*. A similar pressure has been described by Starr[11] which he calls "static blood pressure." Intrinsic blood pressure is not static, however, it will be shown to be a manifestation of a dynamic hydraulic process.

The findings in this study are used in support of a new theory of body hydraulics which incorporates basic physical principles which have been overlooked in older concepts. This theory answers the inconsistencies in the older concepts and increases the understanding of the body as a hydraulic system.

From the Santa Barbara Cottage Hospital, Santa Barbara, Calif.

EXPERIMENTAL PROCEDURE

It is impractical to stop the circulation of the blood by stopping the heart to measure the intrinsic blood pressure, so a method of approximating it, suggested by Dr. A. E. Koehler,[6] was used. He assumed that an arm contained a proportionate sample of the body's arteries, capillaries and veins and that if this vascular bed was isolated from the general circulation the pressure within it, when allowed to equalize, would approximate the intrinsic blood pressure of the body as a whole. The arm contains a convenient vascular sample for study as blood flow to and from it can be readily interrupted.

The blood flow to and from the right arm was stopped instantaneously by inflating a pneumatic cuff around it from a tank containing air under 350 mm. Hg pressure. A cuff 1 inch wide was used. This narrow cuff displaced a minimal amount of blood distalward from underneath it as compared with other cuffs. Narrower tourniquets were found to give identical readings. The sudden inflation from the pressure tanks insured simultaneous interruption of arterial and venous flow. The cuff was placed half way between the shoulder and the elbow joint. The flow of blood beneath the cuff through the bone marrow cavity was found to be insignificant, as the same results were obtained with the cuff over the elbow joint where this is not possible.

Pressures were recorded by a rubber tambour manometer which was connected by plastic tubing and a 20-gauge needle to either the antecubital vein or the brachial artery. The tambour had a mirror mounted eccentrically which reflected a parallel-ray light beam onto a calibrated scale.

Ringer's lactate solution was used to fill the manometer, tubing and needle, so that only two to five drops of blood escaped in recording the pressure. It was found that this amount of fluid did not alter the pressure a measurable amount, therefore it could be ignored. The top of the manometer was placed level with the antecubital vein.

Tests were done with the subjects lying on a level bed without pillows. The right arm was placed in a horizontal attitude with the antecubital vein level with a point midway between the xiphoid and the bed. Subjects reclined in this position for five minutes to stabilize their cardiovascular system before readings were made.

After the cuff was inflated the pressure in the artery decreased and the pressure in the vein increased so that in 15 to 45 seconds they were equal. This was considered to be the intrinsic blood pressure. This pressure then gradually decreased so that it was two-thirds of the initial equalized pressure after five minutes. As the intrinsic blood pressure readings are the same in the arteries and veins, venous punctures only were used in the cases reported below. The highest reading in the vein after occlusion of the circulation is the intrinsic blood pressure and is found 15 to 45 seconds after the cuff is inflated.

Inadequate occlusion of the circulation was recognized if the pressure in the veins continued to rise and did not fall after 45 seconds to 1 minute. There were five subjects whose circulation could not be stopped because of their marked arteriosclerosis, even with the high pressure used in the cuff. Movement of the muscles of the arm during the procedure was eliminated as this motion forces blood from the arteries into the veins and several minutes are then required for retrograde equalization of the pressure through the competent venous valves. Care was taken to have the arm far enough away from the side of the body so that the axillary veins were not compressed. The pressure of clothing in the axilla also was eliminated. Readings taken on the same normal subjects on different occasions under standard conditions did not vary more than 2 to 3 cm. of Ringer's lactate pressure.

Twenty-seven readings were taken to standardize the procedure; these have, therefore, been omitted. The cases below were consecutive readings all taken under standard conditions.

TABLE 1.—*Arterial, Venous and Intrinsic Blood Pressure in Subjects without Shock, Hypertension or Heart Failure*

No.	Name	Sex	Age	Art. BP mm. Hg	Ven. BP (cm. R.L.*)	Intrin. BP (cm. R.L.)
1	E. K.	M	48	110/70	5	16.5
2	D. D.	M	30	124/70	12	18
3	N. S.	F	25	110/70	6	14
4	R. S.	M	28	110/70	8	15
5	A. J.	F	25	110/80	9	17
6	M. F.	F	24	120/70	8	13
7	F. W.	F	40	130/70	7	13
8	E. H.	F	24	105/65	5	14
9	E. B.	M	62	120/60	5.5	17
10	C. B.	F	21	100/70	9	16.5
11	J. P.	F	20	110/70	10	17
12	P. W.	F	23	118/70	9	19
13	S. A.	F	33	100/65	5	12
14	M. M.	M	34	110/65	6.5	15.5
15	J. D.	F	23	100/65	5.5	14
16	D. R.	M	38	120/70	11	15
17	J. M.	M	22	110/75	10	16.5
18	R. A.	M	30	120/70	6	12
19	M. N.	F	21	110/85	9	15
20	J. B.	M	33	118/75	12	18
21	A. M.	F	26	105/65	9	15
22	L. P.	M	33	110/65	11	18
23	D. D.	F	23	120/75	12	16
24	B. W.	M	35	130/80	8	15
25	R. A.	F	32	120/80	10	15
26	P. S.	M	19	110/70	9	17
27	M. Y.	M	22	110/65	9	15
28	P. A.	F	23	110/60	5	12
29	F. F.	F	23	110/70	11	16
30	L. W.	F	23	105/65	8	12
31	B. C.	F	21	100/65	8	15
32	L. H.	M	35	125/80	12	19
33	G. R.	M	29	115/70	11	17
34	B. A.	F	68	130/80	7	18
35	J. C.	F	30	120/75	10	18
36	L. F.	F	28	130/85	10	16
37	L. D.	F	26	120/80	9	17

* In this and other tables R. L. refers to Ringer's lactate solution.

CLINICAL FINDINGS

A total of 103 intrinsic blood pressure readings made on 81 people were used in this study.

Thirty-seven subjects (table 1) who had normal arterial blood pressure and no evidence of cardiac disease, hypertension, hypotension or shock were used to establish the normal intrinsic blood pressure range. It was found to be 12 to 19 cm. of Ringer's lactate solution.

The intrinsic blood pressure in shock and hypotension in five cases (table 2) varied from 4 to 11 cm. of Ringers' lactate solution. Subject 38 had hypotension. It is noted that her intrinsic blood pressure was below the normal range. Subject 39 developed shock postoperatively. She had cold perspiration, tachycardia and an arterial blood pressure of 70/65 mm. Hg. At that time her intrinsic blood

TABLE 2.—*Arterial, Venous and Intrinsic Blood Pressures in Subjects with Hypotension and Shock*

No.	Name	Sex	Age	Art. BP	Ven. BP	Intrin. BP	Remarks
38	A. H.	F	72	75/55	5	10	Hypotension
39	M. S.	F	49	70/65	3	8	Postoperative shock
				110/55	5	13	After transfusions
				130/70	6	16	After recovery
40	A. S.	M	52	50/35	5	11	Postoperative shock
				60/40	5	12	1 hr. later
				Unobtainable	1	5	1 hr. later
					1	4	1 hr. later
					1	3	Expired
41	I. L.	F	56	100/75	6	13	Postoperative no shock
				60/50	5	10	1 hr. later shock
				140/100	6	17	After noradrenalin
				100/80	7	15	½ hr. later
64	M. W.	M	52	(See fig. 4)		11	During shock

pressure was 8 cm. lactate solution. After transfusions and the return of her arterial blood pressure to normal her intrinsic blood pressure was also normal. Subject 40 developed postoperative shock from which he died. As shock became more severe his intrinsic blood pressure fell. Subject 41 had shock after intracranial surgery which was controlled by norepinephrine. Her intrinsic blood pressure paralleled her arterial blood pressure. Subject 64 went into shock from gastrointestinal hemorrhage. As this occurred his intrinsic blood pressure fell from 24 to 11. After the hemorrhage stopped and the shock subsided the intrinsic blood pressure rose to 18 cm. lactate solution. This case represents other hydraulic states and will be referred to again.

Readings on 22 patients with hypertension are shown in table 3. These cases had pressures from 11 to 35 cm. lactate solution. Outstanding in this group is subject 45. He developed hypertension a few days after the onset of carbon tetrachloride poisoning. He presented a picture of lower nephron nephrosis. The high intrinsic blood pressure readings of 32 to 35 cm. were obtained. Several hours before he expired his intrinsic blood pressure had fallen to a normal value of 17 cm. lactate solution, at which time he no longer had hypertension. He at no time had findings suggestive of congestive heart failure or elevated venous pressure.

Eighteen cases of congestive failure are shown (table 4). The intrinsic blood pressures

TABLE 3.—*Venous and Intrinsic Pressures in Subjects with Systolic Arterial Blood Pressures Above 150 mm. Hg*

No.	Name	Sex	Age	Arter. BP	Ven. BP	Intrin. BP
42	F. P.	F	55	190/110	15	25
43	R. L.	M	54	195/125	7	15
44	N. H.	F	80	170/75	9	13
45	S. M.	M	29	190/110	7	35
				205/100	12	34
				170/110	12	32
				100/50	7	17
46	D. M.	F	46	170/100	5	11
47	E. L.	F	89	205/100	10	21
48	H. R.	M	47	210/110	7	21
49	C. O.	M	52	170/110	7	21
50	A. C.	F	40	150/70	12	24
51	E. F.	M	53	200/110	8	20
52	G. B.	M	64	200/110	12	24
53	F. L.	M	50	220/110	11.5	23
54	S. E.	F	53	230/110	3	16
55	J. L.	M	51	150/100	10	16.5
56	B. C.	F	52	190/110	7	17
57	C. C.	M	50	200/100	8	17
58	C. H.	M	45	230/120	7	17
59	M. F.	F	73	160/110	7	14
60	E. B.	F	60	180/110	8	14
61	W. F.	M	45	220/120	7	15
62	G. H.	M	30	150/80	7	20.5
63	R. S.	M	52	170/90	10	34

of the untreated cases were all above the normal. They ranged from 23 to 50. The intrinsic blood pressure in congestive failure patients after treatment resulting in compensation was normal. Case 64 had a myocardial infarction. One week later he developed clinical

TABLE 4.—*Arterial, Venous and Intrinsic Blood Pressures in Subjects Having Congestive Heart Failure*

No.	Name	Sex	Age	Arter. BP	Ven. BP	Intrin. BP	Remarks
64	M. W.	M	52	80/65	27	35	Congestive failure
				105/60	24	34	Treated 24 hrs.
				95/60	13	24	Treated 48 hrs.
				80/60	3	11	Shock from hemorrhage
				90/60	11	21	After transfusions
				100/65	8	18	24 hrs. later, improved
				Expired the next day from myocardial infarction			
65	M. W.	M	39	140/82	20	30	Congestive failure
66	J. V.	M	82	125/80	24	37	Congestive failure
67	A. Q.	M	47	180/140	35	50	Congestive failure
68	H. W.	M	59	130/90	27	38	Congestive failure
				135/95	22	32	Refractory to treatment
69	H. G.	F	32	105/85	22	35	Congestive failure
70	D. D.	M	60	120/75	24	31	Congestive failure
71	E. H.	F	45	180/122	17	27	Congestive failure
				190/120	19	24	Refractory to treatment
72	B. P.	M	55	185/110	24	42	Congestive failure
73	W. S.	M	70	140/60	25	50	Overtreated for shock 12 units blood in 24 hrs.
				180/80	13	30	24 hrs. later after diuretics
				130/60	17	35	24 hrs. later 1 hr. prior to death
74	J. K.	M	69	135/75	15	23	Refractory to treatment
75	C. C.	M	65	120/70	20	40	Congestive failure
76	R. M.	F	31	220/80	17	35	Congestive failure
77	F. T.	M	60	110/80	12	24	48 hrs. after myocardial infarction
				120/75	14	31	24 hrs. later congestive failure now evident
78	J. F.	M	40	150/80	13	21	After compensation
79	J. V.	M	35	105/65	12	17	After compensation
80	H. S.	F	56	95/60	7	13	After compensation
81	J. H.	M	45	195/110	8	13	After compensation

evidence of congestive heart failure. The first reading taken at that time showed an intrinsic blood pressure of 35 cm. of lactate solution. On therapy of diuretics and digitalis this pressure fell in two days to 24 cm. At that time he no longer showed clinical evidence of congestive heart failure. He had been receiving Dicumarol and then had a massive gastrointestinal hemorrhage, followed by shock. His intrinsic blood pressure at that time fell to 11 cm. After transfusions the signs of shock disappeared and his intrinsic blood pressure stabilized at the normal value. He then remained out of both shock and congestive heart failure but died the following day from extension of his infarct. Case 73 was a postoperative patient who was thrown into congestive heart failure by excessive transfusion. Twelve units of blood were given to him within 24 hours. This was in great excess of blood loss. At the first reading his intrinsic blood pressure was elevated to 50 cm. lactate solution. He was digitalized and diuretics were given but no blood was withdrawn. He improved slightly for one day, as is seen by the second readings. The pressures, however, began to rise and the third readings were taken one hour prior to death. Readings on cases 78 to 81 were taken after signs and symptoms of congestive failure disappeared following adequate treatment.

TABLE 5.—*Summary of Intrinsic Pressures*

Description	No. Cases	Intrin. BP
Shock and hypotension (includes 1 case under congestive failure)	5	4–11
Normals	37	12–19
Hypertensives	22	11–35
Congestive heart failure	18	23–50
Totals	81	4–50

Table 5 shows a summary of the findings. Normal intrinsic blood pressure was found to

be from 12 to 19 cm. of Ringer's lactate solution. In pathologic states the intrinsic blood pressures were from 4 to 50 cm. of Ringer's lactate pressure.

Discussion

A model hydraulic system (fig. 1) is shown to demonstrate the physical laws that govern body hydraulics. This system is filled with water and has a variable energy source, E, which forces this fluid into it. There is a variable resistance point, R. One side of the container is a rubber diaphragm which can be tightened or loosened, thereby increasing or decreasing the tone or elasticity of that side. A piston is incorporated in one wall. A circulating pump, X, has both its inlet and outlet in the container.

The pressure at a point P where fluid is not in motion, if hydrostatic pressure is made constant, will increase if either the energy, E, or the resistance, R, are increased and will decrease if either E or R decrease. This is expressed by the formula

$$P = \phi\,(E, R)$$

where E is energy, ϕ is a function, R is resistance and P is pressure.

The circulating pump, X, cannot alter the pressure in the tank as a whole, as expressed by P, as it pumps into the same container that it pumps out of. It can merely elevate the pressure at its outlet by depressing it at its inlet.

Alterations in the tone of the rubber diaphragm will cause very transient changes in P while the size of the container is changing. As soon as the new size of the container is reached P will return to its old value. The same is true of the piston. If it is moved out the pressure will fall until the piston stops at its new position. The pressure will then rise to the original value.

This shows that the pressure in a permeable fluid-filled container is dependent upon only two factors, the energy forcing fluid into it and the resistance to the outflow of fluid. Changes in size, volume, shape and tone or elasticity can cause only very transient changes in pressure. As soon as a new static size is reached the pressure reverts to a function of E and R.

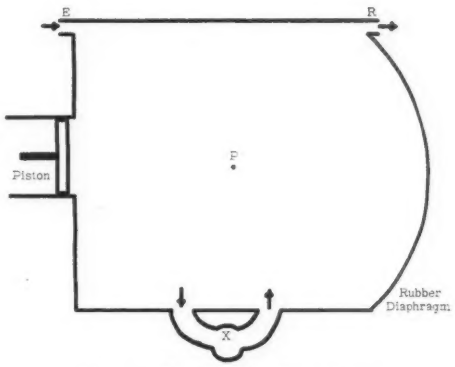


Fig. 1. Model hydraulic system

It has also been shown that circulation of fluid within the container unless it effects E or R is not responsible for the pressure in the container.

The cardiovascular system is a permeable fluid-filled container. Its pressure (referred to as intrinsic blood pressure) is, therefore, expressed by the formula $P = \phi\,(E, R)$. It is evident, therefore, that intrinsic blood pressure, except for transient changes, is dependent on only two factors: (1) the energy which forces fluid into the vascular system and (2) the resistance to the outflow of fluid from the vascular system. The circulation of fluid by the heart, the tone of the vascular system, and the volume of blood have no lasting effects on intrinsic blood pressure.

The E or energy which forces fluid into the vascular system is most likely the change of chemical energy to hydraulic energy which occurs in the endothelial cells lining the vascular system. This energy transports protein and other particles from outside the vascular system through the endothelial cells into the vascular system. R is resistance whereever fluid leaves the vascular system either into the tissue spaces or kidney glomeruli and tubules, or other sites.

In a normal circulatory system, as in Figure 2, the normal intrinsic blood pressure is distributed by a circulating pump, the heart, which elevates the arterial pressure by depressing the venous pressure toward zero. It cannot depress the venous pressure below zero as it is a force and not a suction pump. Figure

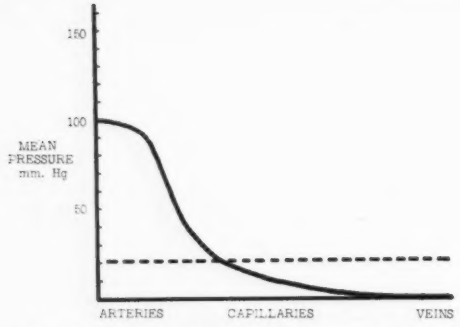


FIG. 2. Normal blood pressure curve (solid line), and normal intrinsic blood pressure (broken line).

2 shows a normal intrinsic blood pressure distributed by a normal heart in a normal vascular system.

If the intrinsic blood pressure is decreased below normal, the arterial pressure cannot be raised as high by the depression of the venous pressure to zero. Shock is the state in which the intrinsic blood pressure is below normal. There are two types of shock. Primary shock results from any transient lowering of intrinsic blood pressure (fig. 3), like the sudden loss of volume or sudden decrease in tone. If during this transient form of shock the endothelium suffers from anoxia before the cardiovascular system is filled again, the energy which forces fluid into the vascular system will decrease and a permanent alteration in intrinsic blood pressure (secondary shock) will ensue.

An elevation of the intrinsic blood pressure above normal allows the heart to elevate the arterial pressure higher by lowering the venous

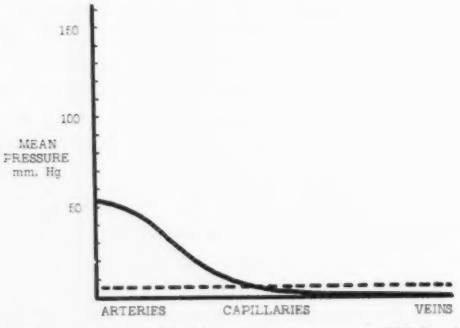


FIG. 3. Shock blood pressure curve (solid line), and low intrinsic blood pressure (broken line).

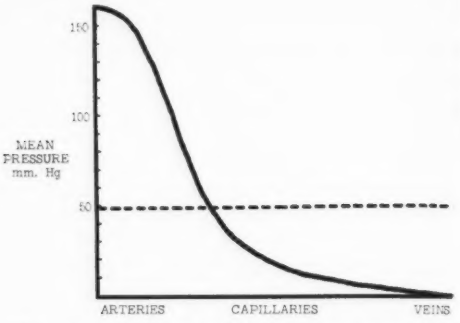


FIG. 4. A hypertensive blood pressure curve (solid line), and a high intrinsic blood pressure (broken line).

pressure toward zero. This accounts for some cases of hypertension, for instance, case 45 and figure 4. Other hypertensions may occur with normal intrinsic blood pressure with altered distribution of it resulting from increased arteriolar resistance. Another type has normal intrinsic blood pressure and normal mean arterial pressure with increased pulse pressure resulting from decreased arterial elasticity. These distinct types and their combinations account for the wide range of intrinsic blood pressures found in table 3.

If the intrinsic blood pressure is raised above the heart's ability to depress the venous pressure toward zero by elevating the arterial pressure, congestive heart failure exists. (See table 4 and fig. 5.) Any heart, no matter how strong, will fail to lower the pressure to zero on the venous side if the intrinsic blood pressure be raised high enough. Similarly, if a heart

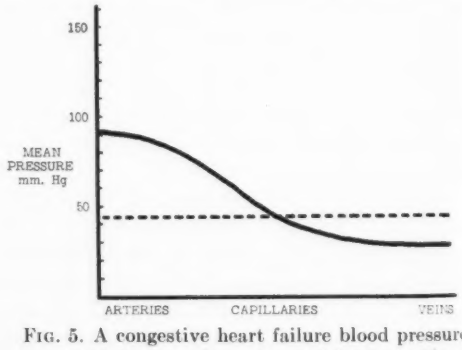


FIG. 5. A congestive heart failure blood pressure curve (solid line), and an elevated intrinsic blood pressure (broken line).

were weakened enough it would fail at a normal intrinsic blood pressure but could be compensated at a lower intrinsic blood pressure. A proposed mechanism of congestive failure is:

Circulatory inadequacy → increased resistance to outflow of fluid in the kidney → increased intrinsic blood pressure above heart's ability to maintain a low venous pressure → over-stretching of heart muscle → further circulatory inadequacy.

The normal circulatory state, shock, hypertension, hypotension and congestive heart failure are determined by intrinsic blood pressure. The control of these states lies in the control of this pressure or more specifically its two factors, E and R. There is need for reanalysis, in terms of intrinsic blood pressure, of all experimental methods used in the past in producing hypertension, congestive heart failure and shock, and all methods used in the past for treating these conditions. This concept opens the road for finding new therapy as it indicates the two factors (E and R) which need to be controlled.

Summary and Conclusions

1. *Intrinsic blood pressure* has been defined and measured in 81 human subjects. Among them were those with a normal cardiovascular state, congestive heart failure, shock, hypotension, and hypertension.

2. Heart failure, shock, hypotension, hypertension, and normal hemodynamics are described in terms of intrinsic blood pressure.

3. Intrinsic blood pressure is shown to be dependent upon two factors, energy and resistance, and expressed by the formula, $P = \phi(E, R)$.

4. An understanding of intrinsic blood pressure is essential to an understanding of the physiology of the cardiovascular system.

Acknowledgments

Acknowledgment is made to A. E. Koehler, M.D., Ph.D. for his assistance, and to H. Weltin, Ph.D., for verifying the mathematical formula.

Sumario Español

1. La presión arterial intrínseca se ha definido y determinado en 81 sujetos humanos. Entre estos habían casos con estado cardiovascular normal, decompensación cardíaca, en choque, hipotensos e hipertensos.

2. Decompensación cardíaca, choque, hipotensión, hipertensión y hemodinámica normal se describen en terminos de presión arterial intrínseca.

3. La presión arterial intrínseca se demuestra depender en dos factores, energía y resistencia, y expresados por la fórmula, $P = \phi(E, R)$.

4. Un conocimiento de la presión arterial intrínseca es esencial para comprender la fisiología del sistema cardiovascular.

References

[1] Bolomey, A. A., Michie, A. J., Michie, C., Breed, E. S., Schreiner, G. E., and Lawson, H. D.: Simultaneous measurement of effective renal blood flow and cardiac output in resting subjects and patients with essential hypertension. J. Clin. Investigation **28:** 10, 1949.

[2] Freis, E. D., Stanton, J. R., Culbertson, J. W., Litter, J., Halperin, M. H., Burnett, C. H., and Wilkins, R. W.: The hemodynamic effects of hypotensive drugs in man. J. Clin. Investigation **28:** 353, 1949.

[3] Gollan, F., Richardson, E., and Goldblatt, H.: Hypertension in the systemic blood of animals with experimental renal hypertension. Arch. Int. Med. **81:** 209, 1948.

[4] Gregory, A., and Levine, W. C.: Studies on hypertension. Arch. Int. Med. **81:** 209, 1948.

[5] Kempner, W.: Treatment of heart disease and of hypertension and arteriosclerotic vascular disease with the rice diet. Ann. Int. Med. **31:** 821, 1949.

[6] Koehler, A. E.: Personal communication.

[7] Landis, E. M., Brown, E., Fauteaux, M., and Wise, C.: Central venous pressure in relation to cardiac competence, blood volume and exercise. J. Clin. Investigation **25:** 237, 1945.

[8] Loofbourow, H. G., Galsfaith, A. L., and Palmer, R. S.: The effect of the rice diet on the level of the blood pressure in essential hypertension. New England J. Med. **23:** 910, 1949.

[9] Paul, O., Bland, E. F., White, P. D.: Cardiovascular disease. Arch. Int. Med. **81:** 209, 1948.

[10] Sapeika, N.: Adrenal cortex and arterial hypertension. Arch. Int. Med. **82:** 263, 1948.

[11] Starr, I.: Our changing viewpoint about congestive failure. Ann. Int. Med. **30:** 1, 1949.

[12] Sweeney, J. S., and Pace, J. M.: Hypertension caused by unilateral kidney disease. Ann. Int. Med. **29:** 370, 1948.

[13] Warren, J. V., and Stead, E. A., Jr.: Fluid dynamics in congestive failure. Arch. Int. Med. **73:** 138, 1944.

Studies Made By Simulating Systole at Necropsy

IV. On the Relation between Pulse Pressure and Cardiac Stroke Volume, Leading to a Clinical Method of Estimating Cardiac Output from Blood Pressure and Age

By Isaac Starr, M.D., T. G. Schnabel, Jr., M.D., S. I. Askovitz, M.D., and A. Schild, Ph.D.

Data derived from experiments on cadavers have been used to test old methods and to design new methods of estimating cardiac stroke volume from estimations of blood pressure, made both by intra-arterial and standard clinical technics. From the data has been derived a method of estimating stroke volume from pulse pressure, diastolic pressure and age, which has reasonably good accuracy in the cadaver experiments, and which is so simple that it could be easily applied by any physician using the apparatus he now has.

DATA secured by the first two authors by simulating systole at necropsy[1, 2] throw light on an old problem, the relation of the blood pressure to the cardiac output. The problem is an important one because measurements of blood pressure, of reasonable accuracy, can be made by any clinician, and if simple methods of estimating cardiac output from these measurements could be devised, and if they proved to be sufficiently accurate, rough estimates of this important aspect of cardiac function would fall within the scope of anyone practicing medicine. It was with this fact in mind that both central and peripheral blood pressures were recorded in almost all of our later experiments in which systole was simulated in cadavers. In this presentation we propose to explore the relationship between the blood pressure itself and the cardiac output, concentrating our attention on simple methods only; more elaborate methods of estimating cardiac output from the contour of the pulse wave will be treated in a subsequent communication.

From the Department of Therapeutic Research and from the Robinette Foundation, Medical Division, of the Hospital of the University of Pennsylvania, Philadelphia, Pa.

This work was supported by a research grant from the National Heart Institute of the National Institutes of Health, United States Public Health Service. Dr. Schnabel is a Markel Scholar in Medicine.

The details of our technic have already been presented in full.[1, 2] We have available data on 56 simulated systoles in which blood was used as perfusing fluid, and in which both femoral and aortic pressures were recorded. We now propose to examine these data with two chief purposes in mind. First, they enable us to assess the simple methods of estimating cardiac output from the pulse pressure proposed by other authors in the past; and second, by subjecting these data to the scrutiny of modern mathematical methods, they permit us to search for different and more accurate ways of making this estimation.

The results have surprised us. A very simple method of estimating cardiac output from pulse pressure, diastolic pressure and age has proved to have, in our data, an accuracy much greater than we expected.

Part I. A Critique of Methods Proposed Previously

Almost exactly 50 years ago, Erlanger and Hooker[3] pointed out the relation between the pulse pressure and the cardiac output. Methods of testing the conception were not available at that time so that the relation could neither be formulated in mathematical terms, nor tested by experiment. But from this suggestion has stemmed a large body of work including, of course, many aspects of our experiments.

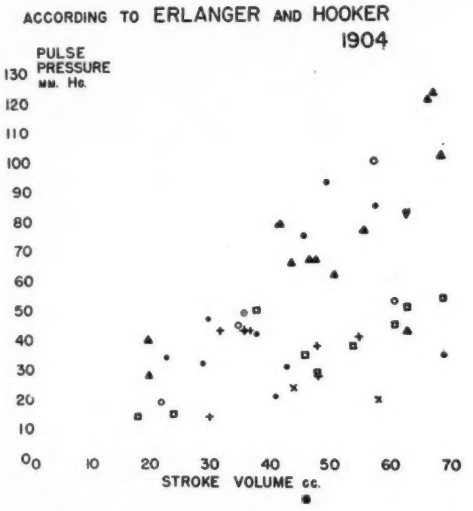


FIG. 1. The relation of pulse pressure to stroke volume (After Erlanger and Hooker[3]). From the edited data (see text) of subjects perfused with blood. Symbols: Circles = data secured on subject P. L.; x's = M. M.; crosses = J. W.; squares = M. L.; triangles = H. Z.

The idea of Erlanger and Hooker concerning the relation between pulse pressure and stroke volume has been tested using the data of our 46 best experiments in which systole was simulated by injecting blood. The results are shown in figure 1. Obviously the relation is not a very close one, and the use of pulse pressure alone would make but a poor method of estimating cardiac stroke volume.

About 25 years later, Liljestrand and Zander[4] suggested that mean pressure must be an important factor in the relation between pulse pressure and cardiac stroke volume, and they undertook experiments which enabled them to compare estimates of stroke volume from an equation containing both pulse pressure and mean pressure, with estimates of stroke volume made by the nitrous oxide method of Krogh and Lindhard.

We have applied the Liljestrand and Zander formula to our data and figure 2 permits a comparison of the stroke volume estimated by this means and the actual stroke volumes. The strong correlation is evident at a glance and the improvement over figure 1 is very

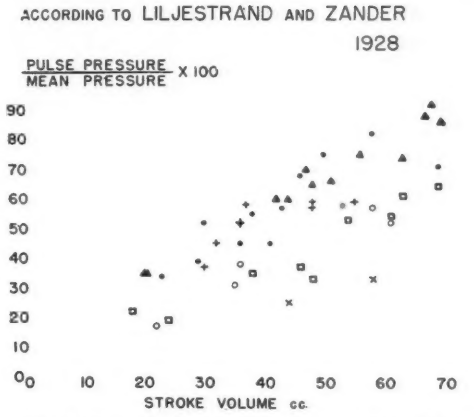


FIG. 2. The relation of pulse pressure divided by mean pressure × 100 to stroke volume (after Liljestrand and Zander[4]). The edited data from subjects perfused with blood. Symbols as in figure 1.

striking; $r = 0.70$, while the level of significant correlation when $p = 0.05$ is only 0.28.

We are much impressed by the extraordinary similarity of the results secured by Liljestrand and Zander to those we attained 25 years later, using methods of estimating both cardiac output and femoral blood pressure in our cadavers, that were certainly more accurate than the corresponding methods which could be applied to the living subject studied by these authors many years ago.

Another 25 years later, a third simple method of estimating stroke volume from pulse pressure was proposed by Remington and coworkers.[5] These authors accepted the conception of Liljestrand and Zander that the absolute height of the blood pressure would influence the relation between stroke volume and pulse pressure, but they used a different method of applying this factor to their calculation. Rather than assuming a ratio, they used experience derived from animal experiments, and comparisons with estimations of cardiac output secured on patients and volunteers by the Fick method with cardiac catheterization, to construct a table by which the expected effect of different pressure levels could be taken into account. Also, in contrast to the two methods previously described, these authors introduced a factor for body size into their equation.

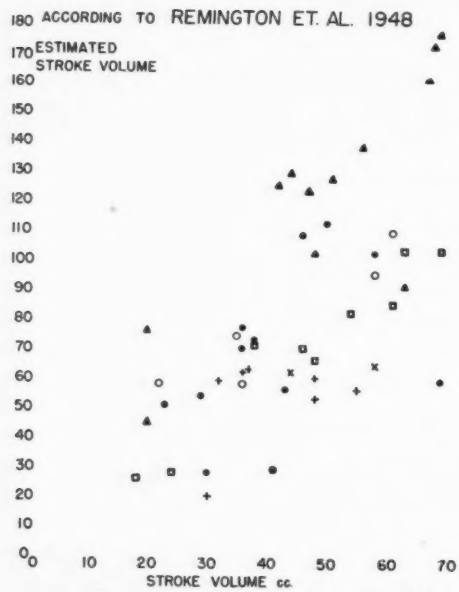


FIG. 3. The relation of the estimate of Remington and co-workers[5] to stroke volume. The edited data from subjects perfused with blood. Symbols as in figure 1.

In figure 3 are shown comparisons between estimates made by the method of Remington and associates[5] and the actual stroke volumes as they were measured in our data. The correlation is significant, $r = 0.63$, but obviously, the estimate usually gives results which are much too high. Also the scatter is large and the method clearly inferior to that of Liljestrand and Zander. Part of the difficulty may well be due to the inclusion of a factor for body size in the equation; in our data the inclusion of this factor in the regression equations helps little if at all, and its use as a factor in Remington's estimate may well be one of the disturbing influences.

PART II. NEW CARDIAC OUTPUT METHODS DERIVED FROM OUR OWN DATA

Concerning the Data

Our experiments[1, 2] provided us with results secured in 56 simulated systoles made in six cadavers in which blood was used as perfusion fluid. The bulk of the raw data has been published elsewhere,[2] the remainder has been placed in table 1. These experiments were done consecutively and no results have been omitted from this series for any reason.

TABLE 1.—*Supplementary Data from Experiments on P. L. Age 47*

Curve No.	Systolic Blow	Padding Number	Aortic B. P.		Femoral B.P.		Stroke Volume	Duration of Eject.	Pulse Wave Velocity
			Syst.	Diast.	Syst.	Diast.			
	ergs $\times 10^{-6}$		*mm. Hg*	*mm. Hg*	*mm. Hg*	*mm. Hg*	*cc.*	*sec.*	*M. per sec.*
3	14.8	3	179	124	179	122	36	0.12	8.3
4	14.8	3	173	122	185	118	35	0.09	8.3
5	32.8	3	230	124	236	120	58	0.13	8.3
6	32.8	3	134	75	160	78	61	0.15	4.6
7	11.0	3	125	100	133	93	22	0.09	6.3

Obviously, if all these data are made the basis of the analysis, bias on the part of the authors is eliminated as far as such a thing is possible. On the other hand, as in every long series of difficult and complicated experiments, certain imperfections were encountered which make us prefer some results to others. Thus we are inclined to edit our series before analysing it and our method of doing this will now be presented.

A chief hazard in taking blood pressure through small tubes inserted into the lumen of a blood vessel is that the outlet of the tube will be partly blocked by impinging on the vessel wall. Our safeguard against such an error lies in the agreement of our central and peripheral measurements of diastolic pressure. If the column of blood in the aorta had been still, exact agreement would be expected, but the blood is moving as the pressure falls, so small pressure differences are to be expected. Inspection of the raw data shows that agreement within a few millimeters of mercury is usual. But occasionally the two measurements do not agree so well, and in such a case we have the right to suspect an error in one of the two measurements, though we do not know which is at fault. We propose, therefore, to omit from our calculations the five experiments in which the central and peripheral diastolic pressure measurements differed by 10 mm. Hg or more; these are: R. R. 6, 7, and 15; and J. W. 10 and 14.

Careful study of the records has detected a technical error in two other experiments. After intra-arterial pressure has been raised to the desired diastolic level by perfusion from the elevated bottle, this is interrupted by clamping the inflow tube before systole is simulated. This sudden interruption of the inflow produces waves which appear in both blood pressure records and in the ballistocardiogram. Perfect technic requires that these waves be allowed to subside before systole is simulated. This is easily accomplished as they are usually damped out within a second, but in two experiments, McD. 6 and 7, systole was delivered too soon and the pressure records are confused by after-vibrations from clamping the perfusion inflow. The distortion is certainly

not great, and might be corrected for, but we prefer to discard the experiments.

It also seems wise to discard two more experiments. In the first, McD. 5, systole is of such long duration that it is altogether outside the range which seems possible in the clinic. We have more doubt about the validity of omitting the data secured in experiment M. L. 8; this experiment was conducted at shock levels of blood pressure and the syringe reading which checks the cardiac output estimation was missed. But we are not altogether sure that these reasons explain why the point is such a bad one, and perhaps our best reason for omitting it lies in the advice of statisticians not to include in a statistical analysis unique points located far from the body of the data even though the exact cause of the error is not discovered.

By thus editing the data we removed nine experiments, leaving 46 to which no objection could be found. These systoles were conducted under extraordinarily diverse conditions, the stroke volume ranging from 69 to 18 cc., the blood pressure from 236/120 to 43/30, so they cover well the ranges likely to be found in resting subjects in the clinics. Indeed, the wide spread of our data seems ideal, except for a difficulty inherent in our method of investigation and out of our control; subjects available for our experiments are almost without exception in the latter half of life.

However, for readers who might doubt the wisdom of thus editing the data, a large part of our statistical analysis has been performed twice, first on the 56 cases without any omissions, and then on the edited series of 47 with central pressure and 46 with peripheral pressure measurements. We ourselves have greater confidence in the latter results and most of the emphasis will be placed on these in this presentation.

Concerning the Methods

The statistical mathematicians have provided a method, known as multiple correlation analysis, ideal for the mathematical study of data such as ours, when one seeks the best method of estimating stroke volume from pulse pressure and other simple measurements. But as we plan to employ these methods in a way seldom, if ever, used before for the solution of a similar medical problem, it seems proper to explain to medical readers some of their advantages and difficulties, if only to acquaint them with the advantages to many types of clinical investigation by technics made possible by the development of the modern electric calculating machines.

It is widely known that, given data of two related items such as pulse pressure and stroke volume as plotted in figure 1, the equation of the best line can be found by mathematical means, and this equation provides the best method of estimating one from the other, if one is unknown. In these computations the best method is defined as that in which the sum of the squares of the deviations of the estimate from the true value—in this case the difference between actual stroke volume and the estimated stroke volume—is at a minimum. Many best lines of this type have been published in this journal; for example, figure 7 of a previous communication from this laboratory,[6] and from the same estimation the error of this method, as defined by the standard deviation, can be readily computed.

For the data given in figure 1, the equation of the best line would contain only one variable, pulse pressure; but an extension of this same mathematical method permits us to calculate best "lines" for data containing more variables. Thus one can determine the best method of estimating stroke volume from two items such as pulse pressure and diastolic pressure; the best method of making such an estimate from three items such as pulse pressure, diastolic pressure and age, and so forth; the limiting factor being solely the bulk of the computation. Most unfortunately, while no single item in the calculation of a multiple correlation is more difficult to compute than the corresponding items used in estimating the ordinary correlation coefficient, the bulk of the computation increases with the square of the number of variables. So, even equipped with a modern computing machine, the bulk of the mathematical work envisioned for this investigation far exceeded the capacities of the first two authors, and they sought help first of Dr. Askovitz, and then of Dr. Schild who, both by training and inclination, were more competent to attack it. The great bulk of the computation fell to Dr. Schild, who employed a Friden automatic electric calculating machine.

An elementary discussion of the methods employed to compute the multiple regression equations given in the tables is to be found in Ezekiel's book[7]; a more advanced and general discussion of these methods and their technics in that of Anderson and Bancroft.[8] In essence, the mathematical problem requires the solution of simultaneous equations set up from the data obtained by experiment. The number of the equations varies with the number of variables considered. Thus to compile equation 21, table 2, one must solve five simultaneous equations with five unknowns; the unknowns being the coefficients of pulse pressure, diastolic pressure, age, body size, and pulse wave velocity. These equations were solved by successive elimination of the five unknowns.

To guard against error, each coefficient was computed at least twice, and in case of disagreement, the computation was repeated until agreement was secured. Additional checks were secured by substituting each of the values found back into the original equation to assure ourselves that they were satisfied.

The estimate of sigma was also computed at least twice in each case; if the results failed to agree the calculation was repeated. Additional rough checks

were provided by observing the size of the sigmas, which should increase with the omission of one or more variables and should all be less than the sigma of the original stroke volumes found by experiment.

Results

The Search for the Best Stroke Volume Method. In table 2 have been arranged the multiple regression equations, made by employing the measurements of aortic arch blood pressure in all the 56 cases in which blood was used, and so without editing the data. Each of the equations should be thought of as defining a cardiac output method, and they have been arranged in order of their accuracy. Some of them are obviously of little merit and we have placed them in the tables not because we expected them to give good estimates of cardiac output, but because they could be readily computed from the calculations required for the more interesting equations, and they serve to round out our study.

TABLE 2.—*Multiple Regression Equations Employing Aortic Arch Blood Pressures. Stroke Volume Related to Central Blood Pressure, Body Surface Area, Age, and Pulse Wave Velocity. Data from 55 Consecutive Systoles (Series not Edited)*

Equation number		σ cc.
1	s.v. = 57.9 − 0.18 Age	14.3
2	s.v. = 53.9 − 1.03 P.W.V.	14.2
3	s.v. = 15.7 + 18.73 S.A.	13.8
4	s.v. = 59.5 − 0.19 D.P.	13.8
5	s.v. = 36.0 + 0.23 P.P.	13.2
6	s.v. = 60.5 − 0.81 P.W.V. − 0.13 Age	14.1
7	s.v. = 60.0 − 0.18 D.P. − 0.15 P.W.V.	13.8
8	s.v. = 15.6 + 0.00 Age + 18.6 S.A.	13.8
9	s.v. = 79.2 − 0.23 D.P. − 0.28 Age	13.3
10	s.v. = 20.1 − 1.53 P.W.V. + 22.32 S.A.	13.3
11	s.v. = 26.4 − 0.21 D.P. + 20.66 S.A.	12.9
12	s.v. = 5.1 + 0.23 P.P. + 18.53 S.A.	12.4
13	s.v. = 55.8 + 0.29 P.P. − 0.37 Age	12.3
14	s.v. = 51.7 + 0.30 P.P. − 0.29 D.P.	11.5
15	s.v. = 52.9 + 0.46 P.P. − 4.05 P.W.V.	10.6
16	s.v. = 17.5 + 0.30 P.P. − 0.31 D.P. + 21.29 S.A.	10.4
17	s.v. = 58.3 + 0.45 P.P. − 0.17 D.P. − 3.22 P.W.V.	10.1
18	s.v. = 93.8 + 0.44 P.P. − 0.43 D.P. − 0.65 Age	8.9
19	s.v. = 84.7 + 0.43 P.P. − 0.42 D.P. − 0.61 Age + 3.78 S.A.	8.8
20	s.v. = 90.7 + 0.50 P.P. − 0.34 D.P. − 1.75 P.W.V. − 0.55 Age	8.4
21	s.v. = 24.6 + 0.51 P.P. − 0.19 D.P. − 3.9 P.W.V. − 0.10 Age + 26.00 S.A.	7.6
	Standard deviation of stroke volumes about their mean	14.5

Units: Stroke volume in cc.; pulse pressure in mm. Hg; diastolic pressure in mm. Hg; age in years; pulse wave velocity in meters per second; body surface area in square meters.

Below the equations given in tables 2, 3 and 4 have been placed the standard deviations of the stroke volumes about their own mean. It is with this value that the standard deviations of the methods given above should be compared, for if any of the proposed methods of estimating stroke volume were altogether without value, its standard deviation would show no improvement over that of the stroke volumes about their own mean. As the standard deviation diminishes, the excellence of the method increases.

Inspection of the results given in table 2 shows many interesting things. The first five equations are of one variable and they all would make poor methods of estimating cardiac stroke volume although it is interesting, and certainly not unexpected, that pulse pressure makes the best single item to employ. The next 10 equations are of two variables; no noteworthy improvement is made before pulse pressure is used, and the best result is secured when pulse pressure and pulse wave velocity are employed. This finding is altogether in accord with generally accepted physiologic conceptions which have been the basis of many attempts to measure stroke volume from pulse pressure and pulse wave velocity.

The next group of three equations, each of three variables, is more interesting, for the results demonstrate that pulse pressure and pulse wave velocity are not the best possible combination. One notes the improvement secured by adding a term for diastolic pressure, as would be expected from the reasoning of Liljestrand and Zander.[4] One finds that a factor related to the size of the subject has

TABLE 3.—*Multiple Regression Equations Employing Aortic Arch Blood Pressures. Stroke Volume Related to Central Blood Pressure, Body Surface Area, Age, and Pulse Wave Velocity. Data from 46 Systoles (after Editing the Series)*

Equation number		σ cc.
22	s.v. = 46.9 − 0.27 P.W.V.	14.4
23	s.v. = 51.1 − 0.10 Age	14.3
24	s.v. = 54.2 − 0.14 D.P.	14.1
25	s.v. = 16.7 + 17.03 S.A.	13.9
26	s.v. = 29.9 + 0.31 P.P.	11.9
27	s.v. = 51.6 − 0.09 Age − 0.14 P.W.V.	14.3
28	s.v. = 52.6 − 0.16 D.P. + 0.41 P.W.V.	14.0
29	s.v. = 13.4 + 0.03 Age + 17.85 S.A.	13.9
30	s.v. = 70.7 − 0.18 D.P. − 0.22 Age	13.8
31	s.v. = 15.7 + 22.4 S.A. − 1.10 P.W.V.	13.7
32	s.v. = 22.4 − 0.17 D.P. + 20.66 S.A.	13.4
33	s.v. = 14.9 + 0.29 P.P. + 9.52 S.A.	11.7
34	s.v. = 44.9 + 0.34 P.P. − 0.27 Age	11.4
35	s.v. = 44.7 + 0.38 P.P. − 0.27 D.P.	10.4
36	s.v. = 45.9 + 0.52 P.P. − 3.67 P.W.V.	9.6
37	s.v. = 52.3 + 0.52 P.P. − 0.18 D.P. − 2.95 P.W.V.	8.8
38	s.v. = 23.9 + 0.36 P.P. − 0.29 D.P. + 13.78 S.A.	8.3
39	s.v. = 90.5 + 0.50 P.P. − 0.45 D.P. − 0.65 Age	7.6(+)
40	s.v. = 100.6 + 0.52 P.P. − 0.45 D.P. − 0.70 Age − 4.59 S.A.	7.6(−)
41	s.v. = 53.6 + 0.55 P.P. − 0.29 D.P. − 0.32 Age + 13.89 S.A. − 2.72 P.W.V.	7.0
	Standard deviation of stroke volumes about their mean	14.4

Units and symbols as in table 2.

TABLE 4.—*Multiple Regression Equations Employing Femoral Blood Pressures. Stroke Volume Related to Peripheral Blood Pressure, Body Surface Area, Age and Pulse Wave Velocity. Data from 46 Systoles (after Editing the Series)*

Equation number		σ cc.
42	s.v. = 48.1 − 0.38 P.W.V.	14.3
43	s.v. = 50.5 − 0.09 Age	14.3
44	s.v. = 19.3 + 15.66 S.A.	14.0
45	s.v. = 57.3 − 0.18 D.P.	13.9
46	s.v. = 28.0 + 0.30 P.P.	11.9
47	s.v. = 51.60 − 0.07 Age − 0.28 P.W.V.	14.3
48	s.v. = 15.9 + 0.03 Age + 16.49 S.A.	14.0
49	s.v. = 18.3 + 21.13 S.A. − 1.14 P.W.V.	13.8
50	s.v. = 55.8 − 0.20 D.P. + 0.43 P.W.V.	13.8
51	s.v. = 74.2 − 0.22 D.P. − 0.22 Age	13.6
52	s.v. = 26.4 − 0.22 D.P. + 20.24 S.A.	13.2
53	s.v. = 14.8 + 0.29 P.P. + 8.41 S.A.	11.8
54	s.v. = 38.6 + 0.32 P.P. − 0.19 Age	11.7
55	s.v. = 42.6 + 0.49 P.P. − 3.55 P.W.V.	9.6
56	s.v. = 47.4 + 0.43 P.P. − 0.40 D.P.	8.9
57	s.v. = 26.4 + 0.42 P.P. − 0.42 D.P. + 13.95 S.A.	8.5
58	s.v. = 54.3 + 0.55 P.P. − 0.32 D.P. − 2.60 P.W.V.	7.5
59	s.v. = 91.0 + 0.54 P.P. − 0.57 D.P. − 0.61 Age	5.9
60	s.v. = 94.4 + 0.54 P.P. − 0.58 D.P. − 0.62 Age − 1.60 S.A.	5.9
61	s.v. = 54.7 + 0.57 P.P. − 0.44 D.P. − 0.31 Age + 13.80 S.A. − 2.30 P.W.V.	5.2
	Standard deviation of stroke volumes about their mean	14.4

Units and symbols as in table 2.

little beneficial effect in contrast to the expectation of Remington and coworkers,[5] and equally to our own surprise. One also notes that the inclusion of a term for age has a most beneficial effect and again to our surprise, that age is more useful than pulse wave velocity.

The use of 4 and finally of all 5 variables further improves the method until in equation 21, the scatter has been reduced to a point where in two thirds of the estimates the error of estimating cardiac output is less than 7.6 cc.

Table 3, giving the regression equations secured after editing the data, shows that this editing has caused but little change from their previous formulation in table 2. Again pulse pressure is the single item most closely related to stroke volume and if one factor only is to be added, pulse wave velocity should be chosen. Again the combination of pulse pressure, diastolic pressure and age (equation 39, table 3) is surprisingly successful and the addition of other terms adds but little. The scatter of results about these best lines in the

edited series is a little smaller than in the consecutive series.

Aortic arch pressure can now be measured in the clinic[9, 10] by passing a small tube into this part of the aorta after inserting it through a needle into the femoral artery. After such a tube has been inserted, pulse wave velocity can be measured with unusual accuracy by first recording pulse waves at the arch, and then, after withdrawal of the tube to that location, in the femoral artery. By comparing the timing of both central and peripheral pulses with electrocardiograms taken simultaneously, pulse wave velocity can be determined by difference. But such a procedure would require both expensive apparatus and skillful technic; and arterial puncture, not always painless in the best hands, may disturb the patient and alter his cardiac output. We were, therefore, interested in learning how accurately cardiac output could be computed from peripheral pressures in our data.

Regression equations employing measurements of peripheral blood pressure are given

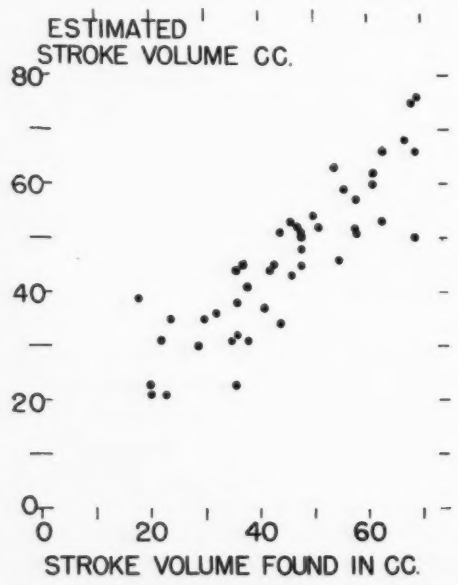


FIG. 4. Relation of stroke volume, estimated from blood pressure and age by regression equation number 59, to actual stroke volume injected. The calculation was made from the edited data from six subjects perfused *with blood*.

in table 4 and in general they agree closely to the corresponding equations in tables 2 and 3. But to our surprise the scatter is less, and so in our data, peripheral blood pressure is to be preferred to central for estimating cardiac output. This finding was unexpected and we have wondered why it should be so. It has long been known that interfering vibrations of high frequency are often found in records of aortic arch blood pressures when one uses a manometer capable of recording them. We find these fine vibrations in a considerable number of our records, superimposed on the pulse wave, and at such times we must exercise judgment in locating systolic pressure. Also, that there may be local pressure changes in the root of the aorta, due to factors other than distention of the compression chamber, has been well demonstrated by Peterson,[11] and such changes might throw off the estimate. However this may be, the excellence of the best of these methods of estimating cardiac output from femoral blood pressure and other data has surprised us.

In many ways, the most interesting method is that suggested by equation 59 (table 4) in which stroke volume is estimated from pulse pressure, diastolic pressure, and age, with an accuracy such that in two thirds of the estimates the error would be less than 5.9 cc. The addition of a term for body size (equation 60) helps not at all, and the further addition of a term for pulse wave velocity (equation 61) helps the scatter only moderately. We therefore regard the cardiac output method indicated by equation 59 as the most interesting of the many indicated by our regression equations.

Naturally we have wondered whether such a formula could be further improved. For example, in our use of the method of multiple regression analysis, we have assumed that the best line is linear. Inspection of dot diagrams such as figure 4 does not suggest that curved regressions would improve the scatter appreciably so we have not explored this aspect further.

Those with physiologic interest will properly ask whether the diastolic pressure is the best measure of arterial distention, and inquire for our reasons for preferring it to the mean

pressure. Indeed, reasons might be cited for adding various fractions of the pulse pressure to the diastolic pressure in a search for the best measurement of the distention of the arterial system. Dr. Askovitz and Dr. Schild saw the means of investigating this question by mathematical methods. When various fractions of pulse pressure are added to diastolic pressure and then correlated with pulse pressure and age, although the equations of the best lines differ, the scatter around these best lines remains identical. Indeed, Dr. Schild produced proof that this similarity of scatter was a mathematical necessity. Three of these equations are given in table 5 and from our data we cannot call one better than another for the estimation of stroke volume.

TABLE 5.—*Multiple Regression Equations Relating Stroke Volume to Peripheral Pulse Pressure, Age, and Diastolic Pressure plus Various Fractions of Pulse Pressure*

Equation Number		σ cc.
59	s.v. = 90.97 + 0.54 P.P. − 0.57 D.P. − 0.61 Age	5.9
62	s.v. = 90.97 + 0.73 P.P. − 0.57 (D.P. + ⅓ P.P.) − 0.61 Age	5.9
63	s.v. = 90.97 + 0.82 P.P. − 0.57 (D.P. + ½ P.P.) − 0.61 Age	5.9
64	s.v. = 90.96 + 0.92 P.P. − 0.57 (D.P. + ⅔ P.P.) − 0.61 Age	5.9

Units and symbols as in table 2.

Tests of the Method on other Data. We had available for the further testing of our group of cardiac output methods a large number of results in which water was used instead of blood to simulate systole, the experiments by which our final technic had been worked up. But we turned to these results with some hesitation because we fully expected that the dynamic pressure-volume relationship, on which the estimation of cardiac output from blood pressure depends, would be different when a fluid of much lower viscosity was used. We expected that, since a viscous solution is harder to force through a tube, the injection of a given amount of blood would cause higher rises of pressure in the compression chamber than if the same amount of water had been injected. According to this reasoning, the cardiac stroke volume formulas in tables 2, 3, and 4 derived from experiments in which blood was employed, should give low results when tested against the data of experiments in which water was used to simulate systole; this is indeed what we find.

A second defect in these experiments tended to produce an error which we judged would be small except when severe hypertension was induced. When water was used, in order to maintain a "normal" diastolic pressure at the instant of "systole," it was necessary to allow the femoral perfusion to continue during "systole." Thus during "systole" the aorta received fluid not only from the heart but also from the femoral perfusion and so the "cardiac output," as measured from the syringe, underestimated the volume the compression chamber actually received. Rough calculation indicates that this error would be a small one except during high hypertension when fluid was being forced into the femoral artery under pressure. Knowledge of this error was a factor in our decision to omit the data from systoles conducted at unusually high hypertensions, and this error is doubtless a factor in the mean difference between our estimate of stroke volume based on the data secured with blood as perfusion fluid and the actual stroke volume measured in the syringes. Also, differences in the rate of this femoral perfusion, varying with the many different pressures at which the systoles were conducted, would increase the scatter of the results. But, despite such drawbacks, the advantage accruing to exact knowledge of the size of the stroke volume seemed so great that we have not hesitated to proceed with the analysis of the experiments in which water was employed.

To avoid the many errors which might be expected to crop up before we had perfected the difficult experimental technic, it seemed wise to confine our attention to the 69 consecutive systoles secured in the last seven cadavers perfused with water, for, by the time these experiments were performed, our technique had been both stabilized and perfected, and, although there was still occasional difficulty in securing satisfactory

ballistocardiograms, we felt that we had mastered the experiments as far as pressure measurements were concerned.

But other difficulties had not yet been completely mastered; indeed throughout the long experience of simulating systole in cadavers using water as perfusion fluid, we had much greater difficulty getting results within the pressure ranges found in the clinic than after we had mastered the technic of using blood.

So we found good reason to reject the data of 19 of these 69 systoles. In 16 the pulse pressure was excessive, ranging from 105 mm. Hg to 225 mm. Hg; and in two, hypertension was extreme, diastolic pressure being over 150 mm. Hg in both. Results from one other systole were rejected because the readings of the cardiac output failed to check. This left us with a sample of 50 systoles whose stroke volumes ranged from 8 to 71 cc., and the peripheral blood pressures from 233/132 to 83/33; so this sample provided ample coverage of the range of values ordinarily found in the clinic in patients at rest. The ages of these subjects ranged from 47 to 77 years.

The clinical and necropsy findings in one of these subjects, P. L., aged 47 and with minimal changes in his aorta, have already been described[1] as he was perfused with blood as well as with water. The pertinent findings in the others were as follows:

Subject 18, Nov. 13, 1951. A. McG. Age, 76; height, 156 cm.; weight, 63 Kg. Blood pressure during life, 120/80 mm. Hg. Clinical diagnosis: malignant melanoma of axilla (removed 1950); metastasis to brain; pathologic fracture first lumbar vertebra. Necropsy diagnosis: malignant melanoma, metastasis to brain and elsewhere. The aorta was moderately atherosclerotic throughout its length and there is considerable calcification around its termination. Aortic diameter above the heart was 2.5 cm.

Subject 19. Dec. 11, 1951. S. S. Age, 49; height, 163 cm.; weight, 62 Kg. Blood pressure during life, 118/64 mm. Hg. Clinical diagnosis: chronic lymphatic leukemia, coronary occlusion. Necropsy diagnosis: chronic lymphatic leukemia, liver and spleen greatly enlarged, coronary atherosclerosis (far advanced). Narrowing of left circumflex coronary artery. The aorta showed moderate involvement by atheromatous plaques. Aortic diameter above the heart was 3.5 cm.

Subject 20. Dec. 19, 1951. J. I. Age, 76; height, 154 cm.; weight, 51 Kg. Blood pressure during life, 148/84 mm. Hg. Clinical diagnosis: carcinoma of esophagus (gastrostomy). Necropsy diagnosis: Squamous cell carcinoma of midesophagus, extension to trachea. Tracheal-esophageal fistula, aspiration pneumonia. The aorta showed moderate arteriosclerosis and at one point in the ascending aorta the intima was roughened and thickened over an area 3 cm. in diameter.

Subject 21. Jan. 2, 1952. E. L. Age, 60; height, 145 cm.; weight, 51 Kg. Blood pressure during life reported to have been normal. Clinical diagnosis: malignant melanoma of left eye (removed). Necropsy diagnosis: arteriosclerotic aneurysm middle cerebral artery, cerebral hemorrhage, pulmonary edema. The aorta was very atheromatous everywhere but the lower half was also ulcerated and calcified. There were also patches of atheroma in the coronary artery and also in the femoral and iliac arteries. Aortic diameter above the heart was 2.4 cm.

Subject 22. Jan. 14, 1952. E. S. Age, 77; height, 153 cm.; weight, 47 Kg. Blood pressure during life, 190/120 mm. Hg. Clinical diagnosis: carcinoma of rectum (resected, left colostomy), hypertensive cardiovascular disease, intraventricular conduction defect, aortic dilatation, benign prostatic hypertrophy, arteriosclerosis, acute cystitis; cystostomy, preliminary to contemplated prostatectomy. Necropsy diagnosis: myocardial infarction, pulmonary congestion and edema, pyelonephritis. The aorta showed moderate atheroma, well marked around the coronary ostia which were narrowed. Aortic diameter above the heart was 3 cm.

Subject 23. Jan. 23, 1952. E. B. Age, 61; height, 184 cm.; weight, 61.5 Kg. Blood pressure during life, 200/150 to 164/100 mm. Hg. Clinical diagnosis: encephalomalacia left cerebral hemisphere, aneurysm left carotid artery within the skull (by arteriogram), epididymitis, osteomyelitis of tibia. Necropsy diagnosis: engorgement and softening of left cerebral hemisphere, aneurysm in region of cavernous sinus. Considerable atheromatous material was present in the aorta just above the aortic valve, other atheromatous plaques were seen throughout the aorta. Aortic diameter above heart was 2.5 cm.

Comparison between estimates of stroke volume made by formula 59 and the actual stroke volumes are shown in figure 5; as was expected, this formula gives low results when water instead of blood is injected, the average error being −5.9 cc. The standard deviation about this mean difference is 9.3 cc.; so, even after correction for the mean difference, the method has a larger scatter than when it is applied to our data secured with blood as

perfusing fluid. But the basic relationship is clearly seen in figure 5 and the method suffices well to distinguish the extremes of cardiac output from the more usual, and so more normal, values. These results, therefore, encouraged us to expect that the method would be useful in the clinic.

A Stroke Volume Formula Adapted to the Standard Procedure for Taking Blood Pressure, Based on the Riva Rocci Method. While arterial puncture is a common procedure, and manometers of great merit are usually available in University Hospitals, the ordinary physician will continue to depend on the standard auscultatory methods of taking blood pressure, and certainly the utility of our formulas would be greatly enhanced if they were adapted to this method. With this in mind we searched the literature without finding data which exactly filled our need. Indeed, we would like to encourage other laboratories to make this adaptation from the run of their own data. We proceeded as follows.

The data of Kotte and associates[12] contain a small series of comparisons between blood pressure estimates made both by the auscultatory method applied to the arm and by puncture of the femoral artery. Unfortunately in their data many of the results secured by the auscultatory method are given as the limits of the range of values and this does not lend itself to statistical analysis. It also seems clear that the present auscultatory technic designed for the arm, when applied to the thigh yields such erroneous results that we were not encouraged to design a cardiac output method based on such measurements.

It seemed wise, therefore, to base our proposed method on auscultatory estimations of blood pressure made in the usual manner on the arm. For this purpose three series of data were available for comparing auscultatory and intraarterial estimates of blood pressure made on the arm, but we decided against employing those of Roberts and co-workers[13] because of the narrow range of the age of these subjects, all of whom were over 70 years of age.

Needless to say, the application of these data to our results must be based on the assumption that intra-arterial brachial and

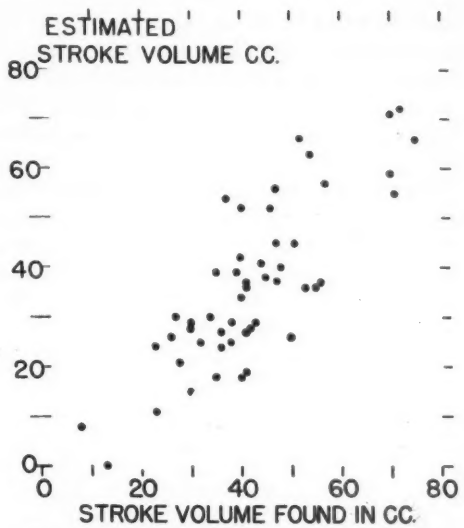


FIG. 5. Relation of stroke volume, estimated from blood pressure and age by regression equation number 59, to actual stroke volume injected. This diagram has been set up by using the edited data from seven subjects perfused *with water*.

femoral pressures are so similar that a correction is unnecessary. There is considerable evidence on this point. The old clinical conception that femoral pressures are much higher is clearly based on an error, the greater thickness of the thigh causing erroneously high results when the auscultatory method is applied to the thigh using cuffs of a width usually employed on the arm. Intra-arterial measurements of brachial and femoral pressures have been compared in only a few cases. Steele,[14] without reporting his data in detail, states that these pressures differed but little, diastolic pressures being roughly the same while femoral systolic pressures were slightly higher. In the data of Kotte,[11] secured in nine persons with hypertension and nine with normal blood pressure, the average brachial pressure was 152/85, the average femoral 158/81. Obviously, diastolic pressures in the brachial and femoral arteries agree closely, and we do not have sufficient data to make it worth while to estimate the small correction for the slightly higher average femoral systolic pressure suggested by the few available results. Therefore, while it seemed that no

great error would be introduced by using for our purposes measurements made on the arm without attempting to correct them, the trend of the data available suggests that the average estimate of stroke volume would be a little low.

The Ragan and Bordley data[15] provide 98 comparisons between intra-arterial pressures in the brachial artery, and the standard auscultatory measurements of blood pressure made in healthy subjects and patients with hypertension.

Accordingly, from these data Dr. Schild calculated regression equations as follows:

Systolic pressure (intra-arterial)
$= 6.08 + 1.04$ *systolic pressure (auscultatory)* (65)

and for this regression $\sigma = 10.3$ mm. Hg

Diastolic pressure (intra-arterial)
$= 4.86 + 0.83$ *diastolic pressure (auscultatory)* (66)

and for this $\sigma = 7.7$ mm. Hg

Pulse pressure (intra-arterial)
$= 8.56 + 1.01$ *pulse pressure (auscultatory)* (67)

and for this $\sigma = 10.9$ mm. Hg

By these equations the pressure measurements secured by the auscultatory method can be substituted into equation 59, and after simplification we have:

Stroke volume (cc.) $= 93 + 0.54$ *pulse pressure (mm. Hg auscultatory)* $- 0.47$ *diastolic pressure (mm. Hg auscultatory)* $- 0.61$ *age (years)* (68)

This represents the way the stroke volume should be estimated from systolic and diastolic pressure secured by the standard auscultatory method using an inflatable cuff 13 cm. broad and taking the beginning of the muffling of sounds as the indicator of diastolic pressure. However, inspection of the results both of Ragan and Bordley[15] and of Steele[14] suggests that the end of the fade-out might be a better measure of diastolic pressure, and indeed this point of view has been adopted by the American Heart Association.[16] In the calculation leading to equation 68 this error is automatically corrected for, but it seemed worthwhile to study data where the position of the end of the fade-out of sounds was recorded.

From the data of Steele, Dr. Schild could derive regression equations relating diastolic pressure measurements made by the intra-arterial and by the auscultatory techniques using the disappearance of the sounds as the criterion. Accordingly from this data we have:

Pulse Pressure (mm. Hg intra-arterial)
$= 14.54 + 0.94$ *pulse pressure (mm. Hg auscultatory) (diastolic pressure at fade-out of sounds)* (69)

For this regression $\sigma = 3.9$ mm. Hg and one notes the smallness of error.

Diastolic Pressure (mm. Hg intra-arterial)
$= -3.2 + 1.03$ *diastolic pressure (auscultatory at fade-out of sounds)* (70)

for this regression $\sigma = 12.5$ mm. Hg

Substituting these values into equation 59 we have:

Stroke volume (cc.) $= 101 + 0.50$ *P.P. (mm. Hg)* $- 0.59$ *D.P. (mm. Hg)* $- 0.61$ *Age (years)* (71)

and with little loss of accuracy this could be rounded out to:

Stroke volume (cc.) $= 100 + 0.5$ *P.P. (mm. Hg)* $- 0.6$ *D.P. (mm. Hg)* $- 0.6$ *Age (years)* (72)

The problem of deciding how the substitution of values secured by the auscultatory method for those obtained by the intra-arterial method would affect the accuracy of the estimate of stroke volume presented difficulties. Needless to say, there were no stroke volumes to compare with the data of Ragan and Bordley, or with those of Steele. After much consideration Dr. Schild proceeded as follows. From equation 59 we have:

Stroke volume (calculated) $=$ *Stroke volume (observed)* ± 5.9 *cc.* (73)

In the calculation of this standard deviation:

$$\sigma = \sqrt{\frac{\Sigma\,[Y_k(\textit{observed}) - Y_k(\textit{calculated by auscultatory methods})]^2}{n}} \quad (74)$$

Y_k being the stroke volume in this instance and $n = 98$, the number of pairs in the Ragan and Bordley data.[14] Since no observed values of the

stroke volume were available to compare with estimates made by the auscultatory method, Dr. Schild considered:

$$Y_k \text{ (observed)} = Y_k \text{ (calculated from intra-arterial data of Ragan and Bordley)} \pm 5.9 \text{ cc.} \quad (75)$$

The right side of this equation was calculated for all 98 intra-arterial observations of the Ragan and Bordley data[14] by the use of equation 59, the plus or minus signs being chosen in such a way as to make any error on the large side. In this way it was found that for equation 68, the standard deviation is calculated to be at most 10.0 cc., for equation 71, at most 9.5 cc. Therefore, we predict that by substituting values secured by the standard blood pressure procedure, using the muffling of sounds as criterion of diastolic pressure, into equation 68, the stroke volume would be estimated with an accuracy such that in two thirds of the estimates, the error would certainly not be greater than 10 cc. Making a similar calculation on the Steele data[13] we find that by using the disappearance of sounds to estimate diastolic pressure one would do a little better, the corresponding figure being 9.5 cc.

But in practice, one should expect to do better than this. The great advantage of a simple method lies in the ease of making multiple estimations, for the use of the mean of several estimates greatly increases the accuracy of any method. Thus, it is certainly not too much to ask any doctor employing the method to take five estimations of blood pressure and insert the average of these values into equation 68 and so reduce the error of this estimate towards the limiting value, 5.9 cc., the σ of equation 59.

The mean estimate of stroke volume in the Ragan and Bordley data[14] by our formula number 68 was 64 cc. Therefore, the coefficient of variation would be $10/64 = 15.6$ per cent without allowing for the improvement to be secured from multiple estimations; these figures permit comparison with the accuracy of other cardiac methods.

Discussion

It seems evident, therefore, that we have derived a simple method of estimating cardiac output from measurements of blood pressure that could be made by any physician. While no claims of high accuracy should be made for it, it seems to be of an accuracy great enough to be of use in the clinic. That it should be as accurate as it is in the cadaver preparations came to us as a surprise, and because the method is based, not on a theory, but on a demonstration made by a new approach to the problem, it has led to changes in our theoretic view concerning the pressure-flow relationships in the circulation.

The theory relating these two in the past has been derived from an analogy with the compression chamber of the old hand pumped organ, the "wind-kessel" theory. This conception was introduced into physiology many years ago to explain the steady flow from the peripheral arteries despite the intermittent pumping of the heart, and this it explains in most satisfactory fashion. Perhaps it was from this analogy also that the idea was derived that the energy of the heart went chiefly to distending the compression chamber, for the simple equation for cardiac work given in text books[17, 18] is:

$$Work = QR + \frac{MV^2}{2}$$

when Q = the volume of systolic discharge, R the resistance or mean arterial pressure, M the mass of injected blood and V the average velocity.

We may visualize this view as follows; let us consider an injection of fluid from a syringe into a partly distended rubber balloon. One notes that in such a situation the energy of the injection is altogether converted into potential energy in the chamber, that the first term of the work equation is large in comparison with the second, and that in the second term of the work equation, the mass involved would be solely that expelled from the syringe, as is postulated in the equation for cardiac work given above. Under such conditions one easily sees that the larger the balloon, or the thinner the rubber of its walls, the less the energy required to inject a given amount of fluid into it in a given time, and the less the pressure in the balloon would rise after such an injection. In such cases the

size of the pressure chamber and its distensibility are determining factors in the pressure-flow relationship.

But this is a special and extreme case. Let us, therefore, consider the opposite extreme and visualize what would happen if one injected from a syringe into a rigid tube filled with fluid, a situation in which none of the energy is converted into potential energy. This is the situation familiar to engineers, and pressure-flow relationships, under conditions of steady flow in rigid tubes, are extensively treated in textbooks of hydraulics. Under such circumstances factors for distensibility of the tube do not enter, but the longer the tube, the greater the mass of fluid which must be accelerated when the syringe is emptied into it, and so the greater the energy required to inject a given volume in a given time. When fluid is injected into a rigid tube the first term of the work equation given above becomes relatively small in respect to the second term, and in this second term the mass to be considered, M, greatly exceeds the mass injected as velocity is immediately imparted to all the fluid in the tube.

We visualize the situation in the body as lying between these two extremes, and unhappily, the kinetics of a pulsating stream flowing down a slightly distensible vessel are so complex that visualization in simple terms is impossible. This was indeed a main reason for our decision to attack the problem by an experiment rather than by attempting mathematical analysis.

Indeed, the same difficulty is frequently encountered by mechanical engineers working with complex systems of rigid tubes, who, finding the usual formulas inadequate for their needs, are driven to direct experiment. The situation in the body is far more complex than in any system of rigid tubes, and among the features to be considered are: (1) the pulsatile nature of the flow, far from the smooth stream lines of flow to which the ordinary equations apply; (2) the distensibility of the vessels, a very difficult feature to handle mathematically; (3) the changing caliber of the vascular bed which brings up special problems, and (4) the diverse nature of the angulation and diameter of the branching vessels, which can be expected to have effects almost impossible to predict. No workable equation combining these four items has ever been presented, and this seems sufficient explanation of the reason why an interpretation of the pressure-flow relationship indicated by our results, in terms so simple that it would be readily understood by any physician, is impossible for us.

Age is an item of considerable magnitude in our important equations and this finding might be interpreted as an effect of increasing size of the aorta, of decreasing distensibility of vessel walls, of increasing resistance due to tortuosity and of roughening of the lining; or of all together, as all may occur as age advances. One has the right to question the implication inherent in our formulas that the effect of age is a linear function especially since the amount of arteriosclerosis, as judged by the gross appearance of the vessels at necropsy, may be so different in persons of similar age. On the other hand, the pathologist concentrates his attention on lesions; many of these are superficial and they usually occupy only a small fraction of the large vascular surface thought of as belonging to the compression chamber. Nevertheless, while it seems that the use of a linear function of age in our equation must give, at best, only a rough approximation of the physiologic state, it is clearly demonstrated that the use of this item considerably reduces the error of our estimates.

After allowance has been made for age, the small effect of pulse wave velocity on the pressure-flow relationship is a finding that took us completely by surprise. In our experiments the pulse wave velocity of single subjects has varied very widely, in one subject from 3.3 to 9.1, in another from 6.1 to 11.1 M per second. Therefore, one cannot take the position that the inclusion of the item for age substitutes for that of pulse wave velocity as a measurement of elasticity of the compression chamber, and so makes the latter less necessary, although it is well known that this velocity tends to increase with age.

Also, although pulse-wave velocity varies with changes in blood pressure in the experi-

ments on single subjects, one cannot think of diastolic pressure as a substitute for pulse wave velocity throughout our data. For example, in systole 11 on subject M. L., aged 43, and in systole 5 on R. R., aged 74, the diastolic pressures were identical, but the pulse wave velocities were widely different in the two subjects. It is the combination of the effects of age and pressure in our equations which makes the further effect of pulse wave velocity so small. But the point of theoretic interest lies in the fact that equation 59, including items for pulse pressure, diastolic pressure and age, yields a much better method than equation 55 which is concerned with pulse pressure and pulse wave velocity. So age and diastolic pressure cannot be thought of as substituting for pulse wave velocity, by using them we do better than by using pulse wave velocity.

Therefore, it seems best to interpret these findings as opposed to the compression chamber theory as it is usually understood. So we have been led to the conclusion that of the two analogies, that of the syringe and the tube is closer to the situation present in the body than has been generally supposed. Indeed, the old analogy between circulation and the organ pumping system is a very poor one. The senior author is old enough to remember such hand pumped organs; the man worked the pump handle slowly; the contained air was itself compressible; it had little mass and was given little acceleration; and its flow encountered a minimum of friction. How different from forcing a viscous incompressible fluid through a tube which stretches only with difficulty, by a force delivered discontinuously and in quick jerks. The compression chamber theory is a static conception, the situation of the body a highly dynamic one. What wonder that expectation based on the former has not been met by direct experiments.

The mathematics involved in the exact analysis of the pressure-flow relationships in pulsatile flow through nonrigid tubes are so complex that it does not seem worthwhile to attack the subject from this point of view, and indeed, it might not be possible. We have attempted to cut the Gordian knot by an experiment the conditions of which seem almost identical with those existing during life.

The success of our method of measuring flow from pressure without factors for body size or pulse-wave velocity, leads us to view the pressure-flow relationship as being far more direct than we had expected. It leads us to a view akin to that of Peterson,[11] that the blood pressure and its changes are related chiefly to the energy needed to accelerate the columns of blood within the vessels and to overcome friction within and at the edge of the moving blood streams. By such a change in viewpoint one can account for the facts developed in the cadaver experiments, facts which lead to the hope that a rough estimate of cardiac output can be made in the clinic far more simply than we had previously believed to be possible.

Summary

Data secured when systole was simulated by injections of blood into the aorta and pulmomary artery of cadavers at necropsy, after giving them a "diastolic pressure" by femoral perfusion, have been analyzed with two purposes in mind.

First, the methods of estimating stroke volume from pulse pressure, suggested by other authors in the past, have been assessed. This resulted in unusually good confirmation of the data and claims of Liljestrand and Zander.[4] The other suggested methods were less accurate when tested against our data.

Second, we sought to improve these methods by subjecting our data to analysis by modern mathematical technics yielding multiple regression equations. We thus estimated "lines" of best fit relating stroke volume to such items as pulse pressure, diastolic pressure, age, body surface area, and pulse wave velocity, both singly and in combination, the resulting regression equations defining both the best way of using such data to estimate stroke volume and the error of the method.

The most interesting method discovered utilized femoral blood pressures secured by arterial puncture (equation 59). It was as follows:

Stroke volume (*cc.*) = *90.97* + *0.5⅓ pulse pressure* (*mm. Hg*) − *0.57 diastolic pressure* (*mm. Hg*) − *0.61 age* (*years*)

The accuracy of this equation in our data was such that in two thirds of the estimates the error was less than 5.9 cc. The addition of factors for body size to this equation improved the method not at all; the addition of pulse wave velocity improved the scatter only a little.

The accuracy of the method was tested against data from 50 simulated systoles in seven other cadavers perfused with water in an early part of our work. As was expected from the differences in viscosity between water and blood, equation 59 underestimated the stroke volume when water was injected. But, after correction for the mean difference, the error of two thirds of the estimates was less than 9.3 cc.

By means of the data from Ragan and Bordley,[15] and because of evidence that intra-arterial femoral and brachial pressures are very closely related, equation 59 has been corrected for use with the standard auscultatory technic of estimating blood pressure, when the point of muffling of sounds is used to indicate diastolic pressure, becoming (equation 68)

Stroke volume (cc.) = 93 + 0.54 pulse pressure (auscultatory, mm. Hg) − 0.47 diastolic pressure (auscultatory, mm. Hg) − 0.61 age (years)

When the disappearance of sounds is used to indicate diastolic pressure this equation is altered, becoming, after rounding out (equation 72)

Stroke volume (cc.) = 100 + 0.5 pulse pressure (auscultatory, mm. Hg) − 0.6 diastolic pressure (auscultatory, mm. Hg) − 0.6 age (years)

The error of this adapted method is estimated to be such that in two thirds of the estimates the error would be less than 10 cc. However, the method is now so simple that multiple estimates are possible; thus, if one used the averages of multiple estimates of blood pressure, the scatter due to random fluctuations would diminish towards a value such that in two thirds of the estimates the error would be less than 5.9 cc.

The new method is so simple that it permits a rough estimate of stroke volume by any doctor practicing medicine with the apparatus and technics he already has. It possesses advantages over the elaborate cardiac output methods in common use that are not limited to a saving of time and expense, for, by avoiding the excitement inherent in elaborate, prolonged and uncomfortable techniques, errors due to emotional disturbance of the subjects' circulation would be in large measure avoided.

Sumario Español

Datos obtenidos cuando sístole fué simulado por medio de inyecciones de sangre en la aorta y la arteria pulmonar de cadaveres durante la necropsia, luego de habérsele suplido una "presión diastólica" mediante perfusión femoral, han sido analizados con dos propósitos en mente.

Primeramente, los métodos para estimar el volumen de pulsación de la presión de pulso, sugeridos por autores en el pasado, han sido evaluados. Esto resultó en una confirmación excepcional de los datos reclamados por Liljestrand y Sander.

Secundariamente, nosotros tratamos de mejorar estos métodos sometiendo nuestros datos a un análisis por medio de técnicas matemáticas modernas producentes de multiples equaciones retrógradas. Así nosotros estimamos las lineas que mejor emparejaban relacionando el volumen de pulsación a otros items como la presión de pulso, presión diastólica, edad, área de la superficie del cuerpo, y velocidad de la onda del pulso, sencillamente o en combinación, las resultantes equaciones retrógradas definiendo ambos la mejor manera de usar estos datos en el estimado del volumen de pulsación y el error del método.

El método más interesante descubierto utilizaba presiones femorales obtenidas mediante punción arterial (equación 59). Era como sigue

Volumen de pulsación (cc.) = 90.97 + 0.54 presión de pulso (mm. Hg.) − 0.57 presión diastólica (mm. Hg) − 0.61 edad (años)

La precisión de esta equación en nuestros datos fué tal que en dos terceras partes de los estimados el error fué menos de 5.9 cc. La suma de factores para tamaño del cuerpo a esta equación no mejoró el método en nada; la suma de la velocidad de la onda del pulso mejoró el esparcir solamente un poco.

La precisión del método se computó en contra de datos de 50 sístoles simulados en siete otros cadaveres perfusados con agua en los comienzos de nuestro trabajo. Como era de esperarse de las diferencias en viscosidad entre agua y sangre, la equación 59 ha sido corregida para uso con la técnica auscultatoria ordinaria para estimar la presión arterial, cuando el momento en que se apagan los ruidos es usado para indicar la presión diastólica, convirtiéndose en (equación 68)

Volumen de pulsación (cc.) = 93 + 0.54 presión de pulso (auscultatoria, mm. Hg) − 0.47 presión diastólica (auscultatoria, mm. Hg) − 0.61 edad (años)

El error en este método adoptado es estimado ser tal que en dos terceras partes de los estimados el error sería menos de 10 cc. Sinembargo, el método ahora es tan sencillo que estimados múltiples son posibles; de manera, que si uno usara el promedio de multiples estimados de presión arterial, el esparcir debido a fluctuaciones casuales disminuiría hacia un valor de manera que en dos terceras partes de los estimados el error seria menos de 5.9 cc.

El nuevo método es tan sencillo que permite un estimado tosco del volumen de pulsación por cualquier médico practicando medicina con los aparatos y técnicas que ya el tiene. Posee ventajas sobre los métodos elaborados de producción total cardíaca en uso común que no estan limitados a economizar tiempo y gastos, evitando la excitación inherente en técnicas elaboradas, prolongadas e incómodas, errores debidos a disturbios emocionales de la circulación de los sujetos podrían en gran parte ser evitados.

REFERENCES

[1] STARR, I., SCHNABEL, T. G., JR., AND MAYOCK, R. L.: Studies made by simulating systole at necropsy. II. Experiments on the relation of cardiac and peripheral factors to the genesis of the pulse wave and the ballistocardiogram. Circulation **8:** 44, 1953.

[2] —, AND —: Studies made by simulating systole at necropsy. III. On the genesis of the systolic waves of the ballistocardiogram. J. Clin. Investigation **33:** 10, 1954.

[3] ERLANGER, J., AND HOOKER, D. R.: An experimental study of blood pressure and of pulse pressure in man. Johns Hopkins Hosp. Reports **12:** 145, 1904.

[4] LILJESTRAND, G., AND ZANDER, E.: Ver gleichen de Bestimmungen des Minuten volumens des Herzens bein Menschen mittels der Stick oxydul methode und durch Blut druck missung. Ztschr. gesamte Exper. Med. **59:** 105, 1928.

[5] REMINGTON, J. W., NOBACK, C. R., HAMILTON, W. F., AND GOLD, J. J.: Volume elasticity characteristics of the human aorta and prediction of the stroke volume from the pressure pulse. Am. J. Physiol. **153:** 298, 1948.

[6] STARR, I., HORWITZ, O., MAYOCK, R. L., AND KRUMBHAAR, E. B.: Standardization of the ballistocardiogram by simulation of the heart's function at necropsy; with a clinical method for the estimation of the cardiac strength and normal standards for it. Circulation **1:** 1073, 1950.

[7] EZEKIEL, M.: Methods of Correlation Analysis. New York, John Wiley, 1950.

[8] ANDERSON, R. L., AND BANCROFT, T. A.: Statistical Theory in Research. New York, McGraw Hill, 1952.

[9] SCHNABEL, T. G., JR., FITZPATRICK, H. F., AND BAZETT, H. C.: Pressure pulses and pulse wave velocities in the aorta and large vessels of man as determined by direct methods. Am. J. Physiol. **159:** 585, 1949.

[10] PETERSON, L. H., DRIPPS, R. D., AND RISMAN, C. G.: A method for recording the arterial pressure pulse and blood pressure in man. Am. Heart J. **37:** 771, 1949.

[11] —, Certain physical characteristics of the cardiovascular system and their significance in the problem of calculating stroke volume from the arterial pulse. Federation Proc. **11:** 762, 52.

[12] KOTTE, J. H., IGLAUER, A., AND MCGUIRE, J.: Measurements of arterial blood pressure in arm and leg. Am. Heart J. **28:** 476, 1944.

[13] ROBERTS, L. N., SMILEY, J. R., AND MANNING, G. W.: A comparison of direct and indirect blood pressure determination. Circulation **8:** 232, 1953.

[14] STEELE, J. M.: Measurements of arterial pressure in man. J. Mt. Sinai Hosp. **8:** 1049, 1941–2.

[15] RAGAN, C., AND BORDLEY, J., III.: Measurements of blood pressure. Bull. Johns Hopkins Hosp. **69:** 526, 1941.

[16] BORDLEY, J., III, CONNOR, C. A. R., HAMILTON, W. F., KERR, W. J., AND WIGGERS, C. J.: Recommendations for human blood pressure determinations by sphygmomanometers. Circulation **4:** 503, 1951.

[17] EVANS, C. L.: Starling's Principles of Human Physiology. Philadelphia, Lea & Febiger, 1952.

[18] WIGGERS, C. J.: Physiology in Health and Disease. Philadelphia, Lea & Febiger, 1944.

Clinical Tests of the Simple Method of Estimating Cardiac Stroke Volume from Blood Pressure and Age

By Isaac Starr, M.D.

The results secured by the simple method of estimating cardiac output, described in the previous paper, have been applied to data already in the literature. Hundreds of comparisons are possible between estimates of cardiac output made by our blood pressure method from values given by the authors, and the results of estimates of cardiac output by some other well known method employed at the same time. The correlations between the results secured by our method and those obtained by Fick, acetylene, ethyl iodide, and nitrous oxide methods are often surprisingly good. There is an unexplained difference in level between the Fick and blood pressure estimates, but not between the blood pressure estimates and those of the three older methods.

As a next step in the investigation of our simple method of estimating cardiac output from blood pressure and age,[1] by formulas derived from experiments in cadavers,[1] it seemed necessary to subject it to test in the clinic. But experiments designed especially for this purpose seemed unnecessary, for a large number of estimates of cardiac output, made by the many methods in use during the last 30 years, have already been reported together with the blood pressures and pulse rates of the subjects tested. Indeed, over 500 instances have been discovered in which it is possible to compare values for cardiac output estimated by our formula from blood pressure measurements made by the authors themselves, with estimates of cardiac output made by some other method. However, one aspect of the situation made me hesitate to undertake this study. Most of the authors have reported the blood pressures of their subjects only incidentally, to indicate whether the subjects suffered from hypertension or not, and so one might properly wonder whether these measurements were made with the care requisite to the use to which we now proposed to put them. Indeed, one does not always know whether the blood pressures recorded were taken under circumstances identical with those under which the cardiac outputs were estimated, or not. And in some reports there is a distressing tendency for the figures given for blood pressure to end in such digits as 0 or 5, a tendency the author finds, alas, in reviewing some of his own work, and which certainly indicates that the highest accuracy was not sought. But despite these difficulties, it seemed wiser to take the data already in the literature at their face value and proceed with a comparison between estimates made by the different methods, especially since the result would be so completely free of bias. From data already in the literature we have estimated stroke volume by our blood pressure method in over 400 instances in which the results of comparable estimates of cardiac output by another method were recorded, and a summary of these results will be given here.

Certainly one might properly have misgivings that our simple scheme of estimating cardiac stroke volume from blood pressure, although working well in cadaver experiments, would work equally well throughout the far greater range of physiologic and pathologic variations to be encountered in the clinic. To use a formula which does not include pulse wave velocity as a measure of the elasticity

From the Department of Therapeutic Research, The University of Pennsylvania, Philadelphia, Pa.

This study was supported by a research grant from the National Heart Institute of the National Institutes of Health, United States Public Health Service.

of the compression chamber at the time of the test is to adopt an unorthodox view. This I was prepared to do, for results secured in cadavers seemed inconsistent with the compression chamber theory as it is usually understood. And it was equally surprising to me to find that the size of the subject, or of his aorta, made so little difference. But preconceived conceptions should have no standing if opposed to the cold logic of the results secured in the cadaver experiments, where stroke volume could be measured with high accuracy, and where both it and blood pressure were recorded directly by methods of a high order of merit. So our formulas for estimating stroke volume, unlike the previous methods proposed for relating blood flow to blood pressure, were not based on a theory but on a demonstration. And the fact that the relations proved simpler than had been anticipated, was, after my surprise had subsided, a cause for rejoicing. Nevertheless, it seemed necessary to undertake the clinical study in the hope of learning what we could of the limitations of the simple ideas developed in the cadaver experiments and of discovering the clinical situations in which these limitations were to be expected.

It was also evident that there were at least two places of weakness in the data from which our blood pressure method had been built up in the cadaver experiments. The first was the lack of data in young persons. When applied to blood pressure measurements taken on young persons the results given by our cardiac output formula are based on an extrapolation from data secured in older subjects. A secondary deficiency was the small number of systoles conducted at high hypertension in the experiments in which blood was used as perfusing fluid, and we were well aware of the lack of agreement between actual and estimated stroke volume in the systoles conducted at very high hypertension, or when pulse pressure was very large, in the experiments in which water was used. So it was hoped that comparison with results secured by other cardiac output methods would throw light on these problems, and help to define the limitations of the method.

Comparisons between Estimates of Cardiac Output from Intra-arterial Blood Pressure and from Other Methods

Comparisons with the Results Secured by the Fick Method

Data secured from Stead's laboratory are particularly suited to this purpose because in these reports blood pressures were secured by an optical manometer connected with a needle in the femoral artery; and thus it is proper to employ our formula 59,[1] first to estimate stroke volume from the pressures recorded, and then, by multiplying the result by the pulse rate, to estimate cardiac output per minute.

A comparison of the results secured in healthy subjects is given in figure 1*A*. In 21 healthy subjects at rest Stead and his coworkers[2] obtained an average cardiac index of 3.98 liters per minute per square meter by the Fick method, with a standard deviation about the mean of 1.36 liters per minute, a coefficient of variation of 34 per cent. Using his blood pressure data and our formula 59, one estimates an average cardiac index of 2.7 liters per minute per square meter, and a standard deviation of 0.50 liters per minute, so that $v = 19$ per cent. The mean of our estimates of basal cardiac output from blood pressure is, therefore, much lower and our data much less scattered than in results secured by the Fick method; but despite these differences the correlation between the two sets of results is highly significant.

In the experiments of Brannon and associates[3] the effect of anemia was investigated, and the relation between the results secured by the two methods is shown in figure 1*B*. Again the estimate from blood pressure is consistently smaller than the Fick estimate, the mean difference being 1.6 liters per minute per square meter. Nevertheless, there is obvious correlation between results secured by the two methods which would be reasonably good were it not for four divergent points, marked with crosses on the dot diagram, each pertaining to a result secured in a case of anemia (hemoglobin 8.6; 10.7; 5.1 and 8.8 Gm.)

which showed an abnormally high cardiac output as estimated by the blood pressure method, but gave values within the normal range by the Fick method, judging by the results secured in the normal subjects described in the preceding paragraph. In favor of the greater correctness of the blood pressure estimate one could point out that the heart rates of three of these four cases were elevated, 100, 94 and 100 per minute; that of the last being 84. Indeed, the blood pressure results suggest that the cardiac output rises much more consistently in anemia than do the Fick results.

In the experiments of Warren and his colleagues[4] the effect of hemorrhage was investigated. In these data the correlations between the estimates of cardiac output made by the two methods is excellent, $r = 0.86$, although the same difference in level appears. There is one interesting difference in result, subject E. S., the only subject to show a substantia

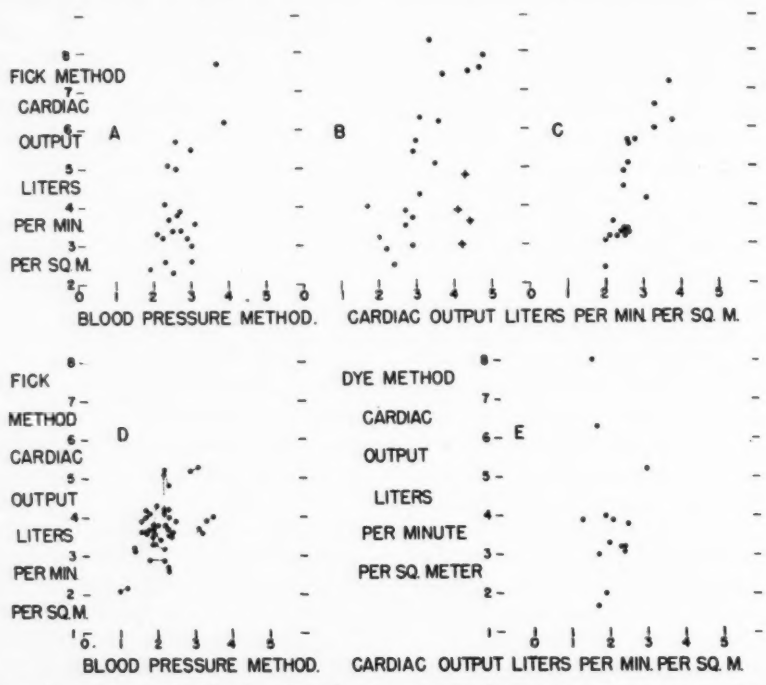

FICK METHOD CARDIAC OUTPUT LITERS PER MIN. PER SQ. M.
A
B
C
BLOOD PRESSURE METHOD.
CARDIAC OUTPUT LITERS PER MIN. PER SQ. M.
FICK METHOD CARDIAC OUTPUT LITERS PER MIN. PER SQ. M.
D
DYE METHOD CARDIAC OUTPUT LITERS PER MINUTE PER SQ. METER
E
BLOOD PRESSURE METHOD.
CARDIAC OUTPUT LITERS PER MIN. PER SQ. M.

FIG. 1. Comparisons of estimates of cardiac output per minute per square meter, made from the blood pressure, and by other methods. The horizontal coordinates define cardiac output per minute as estimated by our blood pressure method and the pulse rate; the vertical coordinates define cardiac output per minute as estimated by the Fick or dye method.

(*A*) Data of Stead and his colleagues,[2] a study of normal subjects. Cardiac output estimates were estimated from femoral intra-arterial blood pressures by formula 59; and by the Fick method. The correlation is significant $r = 0.62$. (*B*) Data of Brannon and co-workers,[3] a study of the effect of anemia. The estimates of cardiac output were made as in *A*. Points marked with a cross are especially commented upon in the text. (*C*) Data of Warren and his associates,[4] a study of the effect of hemorrhage. Estimates as in *A*. Note the strong correlation, $r = 0.91$. (*D*) Data of Cathcart and co-workers,[5] a clinical study concerned with the evaluation of Nickerson's ballistocardiographic method. Cardiac outputs were estimated from auscultatory blood pressures, using the point of muffling as diastolic pressure, by our formula 68, and by the Fick method. Duplicate estimates are joined by lines. The correlation is significant. $r = 0.47$ after correction for attenuation. (*E*) Data of de Wardener and colleagues,[7] a study of the effect of hemorrhage on anesthetized subjects. Cardiac outputs were estimated from femoral intra-arterial blood pressures by formula 59; and by Hamilton's dye method.

increase of cardiac output after hemorrhage by the Fick method, shows a negligible increase in the estimate from blood pressure, a finding consistent with the results secured after hemorrhage in the other subjects. But it should be emphasized that the unexpected finding of this paper, and the chief conclusion of Warren and associates,[4] that a subject could be bled to the point of collapse without a material decrease in his cardiac output, is altogether supported by the blood pressure data.

Other data secured in Stead's laboratory do not lend themselves so well to our purpose, although they deserve mention. The ample data of Hickam and Cargill[5] on the effects of exercise cannot be used because pulse rates are not given, but, with the knowledge that the heart rate can be expected to rise during exercise, inspection of the data indicates that correlation between estimates from blood pressure and from the Fick method is to be expected. On the other hand, when one inspects the data on the effects of tilting given by Hickam and Pryor,[6] although the results secured by the two methods of estimating cardiac output cannot be directly compared as the height and weight of the subjects are not given, it is easy to see that the agreement would be very poor. The average of both methods indicates a diminished stroke volume on tilting to 60 degrees, but the diminution is much larger in the Fick estimates. As the position of the subject approached the vertical, the output per minute fell in 17 of 18 tests according to the Fick results, while it diminished in only 8 of the 18 tests according to the estimates made from blood pressure.

Comparisons with Results Secured by the Dye Method

The data of de Wardener and coworkers[7] permit 14 comparisons between estimates made from intra-arterial blood pressure by formula 59 and by Hamilton's dye method of estimating cardiac output. These results were secured in experiments on the effects of hemorrhage during anesthesia, and figure 1*D* shows the results. Again the blood pressure estimates are at a lower level. What would be good correlation is spoiled by two extremely divergent points. According to the results secured by the dye method, the cardiac output per minute of each of these subjects at this time was much larger than any other value found in the rest of the experiments, despite the fact that the pulse rates were only 55 and 47 per minute. Indeed, these two stroke volumes, as estimated by the dye method, are so huge, 220 and 320 cc., that one is inclined to bet on the greater accuracy of the estimates from blood pressure, which give results at a level consistent with that found under similar conditions in the other experiments of this series.

Comparisons between Estimates of Cardiac Output Made from Blood Pressures Taken by the Auscultatory Method, with Those Made by Various Other Cardiac Output Methods

Comparisons with Results Secured by the Fick Method

As soon as the ordinary clinical method of taking blood pressure is used as the basis for an estimation of cardiac output from our formula, a much larger error must be expected, but it seemed proper to make further tests of our method in the ample data already in the literature in which auscultatory blood pressures were recorded in conjunction with estimations of cardiac output by some other method. Almost ideal for this purpose is the splendid body of data compiled by Cathcart and associates,[8] the qualification being inserted solely because blood pressures were taken in conjunction with the ballistocardiograms—blood pressure being employed in Nickerson's formula for measuring cardiac output from these records—rather than under the exact conditions in which the blood and gas samples required for the Fick estimate were secured. In presenting this comparison here we shall consider only the 46 results in 23 cases in which duplicate estimations are reported, because this feature, so seldom accomplished by those working with the Fick method, seems so vitally necessary not only to permit detection of technical errors, but also to demonstrate that the subject is actually in the steady state

that is essential for accuracy of the results, despite the character of the experiment, which, requiring cardiac catheterization, arterial puncture and breathing through a mask, seems certainly sufficient to disturb most conscious patients.

Figure 1*D* shows the results of such a comparison. The correlation is highly significant, $r = 0.44$, while a value of 0.291 is significant for $p = 0.05$, though the agreement is certainly not of a high order. The agreement of duplicates by both methods is unusually good, the test-retest correlation coefficients being 0.91 for the Fick duplicates and 0.96 for those estimated from blood pressure. Correcting for the variation inherent in each method as judged by the deviation of duplicates—called by the statisticians correcting for attenuation—the correlation between the results secured by these two methods rises from $r = 0.44$ to $r = 0.47$.*

Comparing the stroke volume as estimated by the two methods, one finds that the standard deviation about the regression which minimizes the Fick values is 21 cc. This is to be compared with the value of 10 cc., which is our estimate of the maximum standard deviation if an accurately measured stroke volume, as in the cadaver experiments, could be estimated from blood pressures determined by the auscultatory method; so apparently each method contributes about the same amount to the differences between the results.

Despite this fairly satisfactory correlation, the marked difference in the level of the results, encountered in comparisons made from data secured in Stead's laboratory[1, 2, 3] persists in these data also. In the comparison permitted by the data of Cathcart and coworkers[8] there is an additional factor which might make the results of the estimate of cardiac output from blood pressure too low; by using formula 68 we have assumed identity of radial and femoral pulse pressures while the scanty data[9] on the subject, too few we believed to base a satisfactory correction upon, indicated that the femoral pulse pressure was actually somewhat larger. But we can correct our formula by the means of the data available securing:

$$\textit{Stroke Volume (cc.)} = 93 + 0.62\ \textit{pulse pressure (mm. Hg)} - 0.45\ \textit{diastolic pressure (mm. Hg)} - 0.61\ \textit{age (years)} \quad (76)$$

When this formula is applied to the data of Cathcart and associates, the estimates of stroke volume from blood pressure are a little larger, but the gross difference between these and the Fick estimates persists, the average value of the former being almost exactly two thirds of the average of the Fick estimates. It is perhaps of interest that this lower level corresponds closely to that of the average of estimates of stroke volume made by Cathcart and colleagues[8] from the formula Nickerson employs for this estimate from his ballistocardiograms, and it was in conjunction with the taking of the ballistocardiograms that the blood pressure was determined. But our estimates of cardiac output from blood pressure correlate much better with the Fick results than with the estimates of cardiac output made by Cathcart and co-workers[8] using Nickerson's methods, and the chief conclusion of this paper, that the latter are of no value for estimating cardiac output in clinical work, is supported by our data.

Comparisons with Results Secured by the Acetylene Method

Figure 2*F* and *G* are concerned with Grollman's experience[10] with two subjects at sea level, during a stay at Pike's Peak and after returning to the base of the mountain. The agreement between results secured by the two methods is striking. Both methods give extremely consistent values at sea level, those of the acetylene method being slightly more so. On reaching the top of Pike's Peak the basal cardiac output increased, as is shown by both methods, but after a few days residence on the peak it diminished somewhat, as both methods show. At the base of the mountain the results were closely similar to those at sea level.

The greater changes in cardiac output produced in one subject by breathing low

* It is of interest that if one omits the data from the 6 pairs in which the duplicate Fick estimates diverge most widely, the correlation of the remaining 34 estimates rises to $r = 0.57$, without correction for attenuation.

oxygen mixtures in a series of experiments are plotted in figure 2*H*, where the correlation between results secured by blood pressure and acetylene methods is impressive, $r = 0.85$.

Unfortunately, in much of the rest of Grollman's data[11] the ages of the subjects are not given. I have, however, used his data on the effects of typhoid vaccine[12] by assigning to the medical students used as subjects the age of 23 years, which is the average age in our school of the class Grollman taught in Johns Hopkins. Obviously to be wrong by a few years would make little difference in the results. The comparison is shown in figure 2*I*. Again there is impressive similarity between the magnitude of cardiac output estimated by acetylene and blood pressure methods when the subjects are at rest and afebrile. Both methods show the increase of cardiac output when fever developed but there is somewhat more scatter, and there is one marked divergence of result, the blood pressure method indicating a great increase

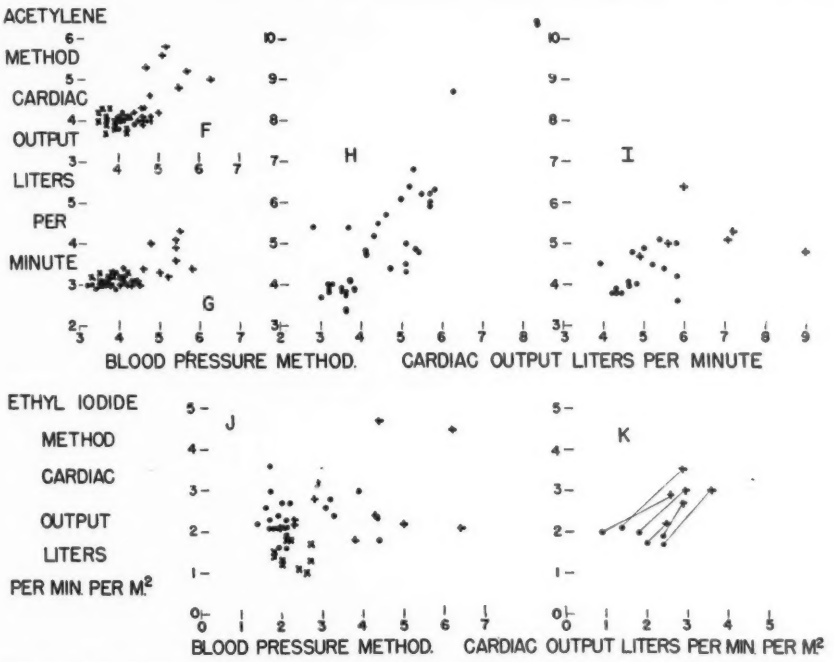


FIG. 2. Comparisons of estimates of cardiac output per minute made from blood pressure (horizontal coordinates) and by two of the older cardiac output methods (vertical coordinates).

(*F*) Grollman's data,[10] basal cardiac outputs of subject A. G. *Dots*, from results at sea level; *crosses*, results secured on the top of Pike's Peak; *x*'s, after return to the base of the mountain. Cardiac output per minute was estimated from auscultatory blood pressures and formula 68; and by the acetylene method. (*G*) Grollman's data,[10] subject L. C. G. at sea level, on Pike's Peak, and at the base of the mountain. Methods and symbols as in *F*. (*H*) Grollman's data,[10] subject A. G. in a series of experiments at sea level concerned with the effect of breathing gas mixtures low in oxygen. Methods as in *F*. Note the excellent correlation between the two methods, $r = 0.85$. (*I*) Grollman's data,[12] experiments concerned with the effect of fever, induced by typhoid vaccine, on healthy medical students. Methods as in *F*. Estimates made while the subjects were febrile are marked with *crosses*. (*J*) Data of the author and his collaborators.[14] Estimates from auscultatory blood pressures and formula 68; and by the improved ethyl iodide method. *Dots*, results secured on healthy persons; *X*'s, results secured on hospital patients judged to have normal circulations; *crosses*, results secured on cases of hyperthyroidism. (*K*) Data of the author,[15] effect of injection of epinephrine on hospital patients. *Dots*, results secured before and *crosses*, results secured during the action of the drug. Results secured on the same subject are joined by lines.

in cardiac output while the acetylene method shows no increase over basal values. Interestingly enough the subject at the time of these estimates had the highest temperature and the fastest pulse rate encountered in the series of experiments, so we have another instance in which, when the blood pressure estimate of cardiac output disagrees with that of a more elaborate and difficult method it is the former that is more consistent with the rest of the data.

The results of this set of comparisons can be summarized only by saying that in Grollman's data the two sets of results are extraordinarily similar.

Comparison with Estimates by the Ethyl Iodide Method

The improved ethyl iodide method was the first cardiac output method which could be applied to subjects without requiring their intelligent and skilled cooperation, so it was the first method to be widely employed in the clinic and comparisons between its results and those secured by the blood pressure method can be made in several hundred instances.[13, 1] A sample of over 50 of these was taken for study.

Figure 2*J* shows comparison of results secured by both methods in a group of healthy persons, a group of hospital patients with circulations judged to be normal from clinical data, and in 10 cases of hyperthyroidism. The average levels of the two sets of results secured in healthy persons are very similar, the mean difference being only 2.8 cc., but the scatter is larger than in the comparison with the acetylene method. The root mean square of the deviations from the mean difference is 23 cc. In results secured in pa-

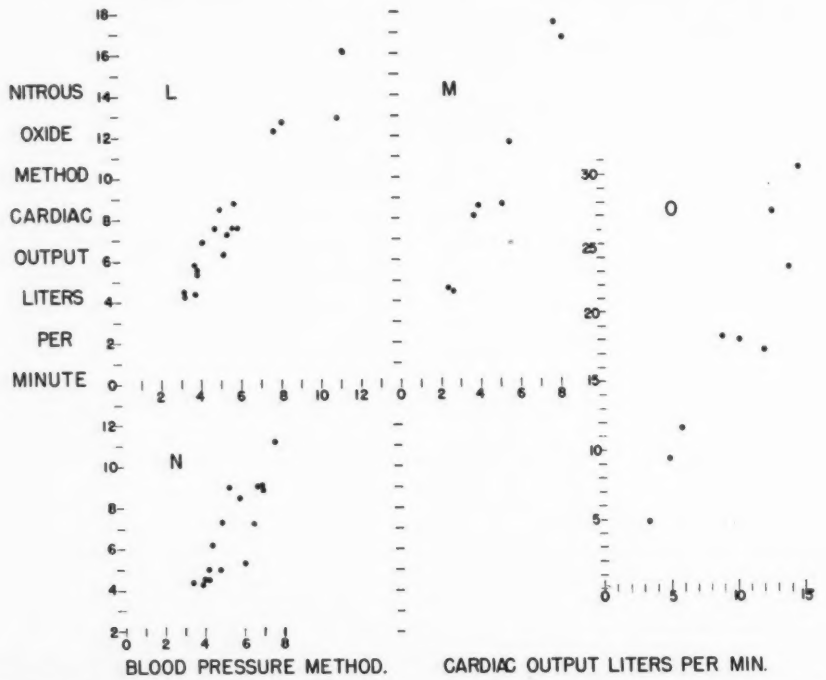


FIG. 3. Comparisons of estimates of cardiac output per minute made from blood pressure (horizontal coordinates); and by the nitrous oxide method of Krogh and Lindhand, (vertical coordinates). Data of Liljestrand and Zander[16]; the subjects sat on a bicycle ergometer or rode at various levels of work. Estimates of cardiac output were from auscultatory blood pressures and formula 68.

(*L*) Subject G. L., a normal subject. Note the surprising correlation, $r = 0.95$. (*M*) Subject K. E. Ek, a case of heart block; $r = 0.97$. (*N*) Subject U. von E., a normal subject; $r = 0.88$. (*O*) Subject H. B., a normal subject; $r = 0.93$.

tients with hyperthyroidism the scatter is still larger. In four of these patients the results secured by both methods indicated a cardiac output within the normal range, in two patients the cardiac output was judged to be far in excess of normal by both methods, so in these six the agreement between results secured by the two methods is reasonably good. But in four cases of hyperthyroidism the circulation was judged to be normal by the ethyl iodide method, but to be clearly greater than normal by the blood pressure estimates. So here again we have a situation in which the blood pressure estimates are more in line with expectations from other sources.

In figure 2*K* have been placed results secured when adrenaline was given to six subjects.[15] The increased circulation occurring after adrenaline is shown clearly in every case by both methods. Both methods yield quite similar results if the data secured before adrenaline is averaged, and also if that secured after adrenaline is averaged, but in most individuals the result of the two methods agree poorly.

Comparison with Estimates Made by the Krogh and Lindhard Method

The four exercise experiments made by Liljestrand and Zander[16] were ideal to compare results secured by the two methods and the data for each of the four subjects has been plotted in figure 3. The correlation in each case is so unexpectedly good that the author was taken by surprise. The results secured by the two methods agree closely as to the resting level of cardiac output in one of the three healthy subjects, but in the other two the results secured by nitrous oxide average a little larger, but the use of formula 76, which allows for possible differences between femoral and brachial pressures brings the levels together. The difference in level is more noteworthy in the patient with heart block, K. E. Ek., who, with a pulse rate in the thirties, was estimated as having a normal resting cardiac output per minute by the nitrous oxide method and a somewhat subnormal output by the blood pressure method. But it need hardly be repeated that the correlation is extraordinary for the subjects individually; and $r = 0.94$ for the group of three healthy persons taken together, while a value of $r = 0.29$ is significant for $p = 0.05$.

To summarize all the foregoing findings, the data has been presented in a somewhat different light in table 1. Correlation coefficients have been included in the foregoing discussion because they seemed appropriate, and to be expected, but in many ways they constitute an inferior method of investigating the relation

TABLE 1.—*Stroke Volume Regression Equations, Standard Deviations about Regression Lines and Coefficients of Variation*

Data	Regression Equation	σ_{yx}	V
		cc.	
Starr et al.[1] (Cadaver exps.; formula 59)	S.V. (measured directly) = 91 + 0.54 P.P. − 0.57 D.P. − 0.61 Age	6	13%
Starr et al.[1] (Cadaver exp. results adjusted for the auscultatory B.P. method. Diastolic pressure at muffling of sounds; formula 68)	S.V. = 93 + 0.54 P.P. − 0.47 D.P. − 0.61 Age	10	16%
Warren et al.[4] (Hemorrhage exp.)	S.V. (Fick method) = 1.5 S.V. (formula 59) + 8.9	20	19%
Cathcart et al.[8] (Resting patients)	S.V. (Fick method) = 1.02 S.V. (formula 68) + 39.6	21	22%
Grollman[10] (Breathing air and low oxygen mixture)	S.V. (Acetylene method) = 0.45 S.V. (formula 68) + 43	10	14%
Liljestrand and Zander[16] (3 normal subjects at rest and during exercise)	S.V. (Nitrous oxide method) = 1.81 S.V. (formula 68) − 25.9	21	20%

S.V. = stroke volume in cc.; P.P. = pulse pressure in mm. Hg; D.P. = diastolic pressure in mm. Hg; age in years. σ = the standard deviation about the regression minimizing the deviations of the results of the elaborate methods. V = σ divided by the mean value of the elaborate method.

of the results of one method to those of another, and indeed, they may mislead the unwary. Therefore, confining our attention to the data best suited to the purpose, the regression equations for stroke volume and the standard deviations around the regression, given (under σ) in absolute values and (under V) in percentage of the mean estimate made by the elaborate method, are given in table 1.

At the head of table 1 is given the scatter of the estimates of cardiac output from blood pressure and age about the true values found in the cadaver experiments, below have been placed the scatter of the blood pressure estimates about the results of four elaborate cardiac output methods. A comparison of the magnitude of these standard deviations is most illuminating. One sees at once that our results correspond most closely to those of the acetylene method in the experiment studied, the scatter about the regression being similar to that which was estimated for our method from theoretical conceptions.[1] However, in this experiment[10] Grollman used only one subject, himself, and undoubtedly this fact has greatly reduced the scatter. Indeed, in the data shown in figure 2 it is obvious that the scatter increases when additional subjects are employed, so these results do not mean that the acetylene method is necessarily superior to the other methods which were used on a number of subjects in the experiments analyzed. Nevertheless, the agreement between the results of our method and those of the acetylene method in this experiment is nothing short of remarkable. Grollman's method required trained cooperation of the subject, and undoubtedly he himself was most adept at it.

Table 1 shows that the Fick and nitrous oxide methods gave almost identical scatter about the regression, which is about twice the amount we estimate to be inherent in the blood pressure cardiac output method when the auscultatory method of taking blood pressure is used.[1] This increase is to be attributed to the errors inherent in the elaborate methods themselves; indeed this difference is of the order of magnitude of the "accuracy" of the Fick procedure as defined by duplicate estimations.

It is of interest to point out that the taking of intra-arterial femoral blood pressures in the experiments of Warren and his colleagues[4] has not led to the expected diminution in the scatter; a possible reason for this may be that the tip of the cardiac catheter was not advanced beyond the tricuspid valve in the experiments from Stead's laboratory, while in the experiments of Cathcart and co-workers,[8] the tip was in the pulmonary artery, which should secure a better mixed sample and so greater accuracy. Perhaps in the experiments from Stead's laboratory the gain in accuracy of the blood pressure method from intra-arterial measurements was cancelled by the diminished accuracy of the Fick estimate; but, in any event, while the slopes of the regressions are somewhat different, the scatter of our estimate about the results of both versions of the Fick method is very similar. The larger correlation coefficient pertaining to the data of

TABLE 2.—*Cardiac Output Regression Equations, Standard Deviation about Regression Lines, and Coefficients of Variation*

Data	Regression Equation	σ	V
Warren et al.[4]	C.O. (Fick) L./min./M.^{2} = $\frac{1.91 \text{ (S.V. by formula 59)} \times \text{P.R.}}{\text{body surface area}} - 0.68$	0.8 L./min./M.^{2}	19%
Cathcart et al.[8]	C.O. (Fick) L./min./M.^{2} = $\frac{0.58 \text{ (S.V. by formula 68} \times \text{P.R.)}}{\text{body surface area}} + 2.5$	0.6 L./min./M.^{2}	16%
Grollman[10]	C.O. (Acetylene) L./min. = 1.08 (S.V. by formula 68 × P.R.) + 0.2	0.88 L./min.	17%
Liljestrand and Zander[16]	C.O. (Nitrous oxide) L./min. = 1.92 (S.V. by formula 68 × P.R.) − 2.63	1.36 L./min.	14%

Data as in table 1. C.O. = cardiac output. S.V. = stroke volume in cc. P.R. = pulse rate per minute. σ and V as in table 1.

Warren and associates[4] is due to the fact that, in these experiments, the range of values is much greater than in the Cathcart data, which dealt altogether with resting subjects.

Finally, in table 2 have been placed the regression equations for cardiac output applicable to the data given in certain of the figures.

Discussion

These studies leave little room for doubt that results secured by our blood pressure method of estimating cardiac output, conceived and designed as a rough method, correlate well with those obtained by many other methods under a wide variety of conditions. Indeed, it seems evident that, in every one of the series illustrated in the figures, the same conclusions must be drawn when cardiac output is estimated from the blood pressure measurements by our formula as were indeed drawn by the authors from the results secured by the elaborate cardiac output methods they employed. But despite this surprising correlation there are some conspicuous differences in results which must be pointed out and discussed.

The goal of a cardiac output method useful in the clinic can be properly approached from two directions. In one, everything is sacrificed to the aim of securing the highest accuracy obtainable, and this has been the philosophy inspiring those who, with great skill and boldness, have developed the Fick method, by means of cardiac catheterization, to its present usefulness[17]; and a much similar aim has also inspired those who labored with the many difficult and time consuming cardiac output methods employed in the past. But there is a second approach which has always seemed equally proper to the author; that of first designing methods so innocuous that they do nothing to disturb the subject, and so simple and practicable that any physician can operate them, and then searching for their limitations. Obviously, our method of estimating cardiac output from blood pressure and age belongs in the latter category, and a chief aim of this study was to compare the results secured by our simple method with those obtained by much more elaborate procedures in the hope that the limitations inherent in the former method could be defined. The accomplishment of this aim would have been simple enough if one had knowledge that the accuracy of the elaborate methods was clearly superior to that of the simple method. But do we have this knowledge? With the results before me, I am by no means certain that we do. The situation, as I see it, is as follows.

When the wide spread of the data favors such investigations there is always significant correlation between results of our estimates of cardiac output per minute from blood pressure, age, and heart rate, and the results of cardiac output estimates made by the Fick, acetylene, ethyl iodide and nitrous oxide methods. In some of these situations the correlation is amazingly good, especially when one recalls that the blood pressure data were collected without knowledge of the purpose to which they have been applied in this paper.

There is, however, a very marked difference in level when estimates of cardiac output made from blood pressure are compared with the results secured by the Fick method, or by the dye method. When compared with results secured by acetylene, ethyl iodide and nitrous oxide methods, this difference is absent or minimal; so, completely to the surprise of the author, the results support the cardiac output levels for resting subjects characteristic of the older, rather than of the newer, technics. But unable to point with certainty to a defect in the Fick procedure to which the difference can be attributed, one must first do some searching of soul regarding the accuracy of the blood pressure procedure. Certainly it is accurate enough in the cadavers, in experiments in which cardiac output could be measured with exactitude, but would it be as accurate when applied to the living?

It is often the philosophic dilemma of quantitative scientific work that, in order to make the accurate measurements we require, we must create conditions different from those in which we plan to apply our method. Thus our blood pressure method is based on experiments made in cadavers, because in these the

cardiac output and many other cardiac functions could be measured with an accuracy not to be approached in experiments on living men or animals. Also in favor of this means of attack is the anatomic similarity of the conditions of our tests to those in which we plan to work, and one would certainly expect that the forces required to accelerate the blood column and the resistance due to pressure and friction would be similar in both the living and the recently dead. Physiologists have not hesitated to apply the results of measurements of arterial elasticity made on aortic rings removed from the animal to conditions existing in the aorta during life[18, 19]; indeed, muscular contraction is readily demonstrated in such rings. Similarly, signs that all vital activity had not ceased were sometimes encountered in our experiments. In addition, surgeons have successfully used as arterial grafts pieces of aorta taken at necropsy many days previously. But despite these aspects favorable to our preparation, the question must be raised; does not some vasomotor effect, ceasing at death, so change the distensibility of the compression chamber during life, that a given stroke volume delivered during life causes a smaller increment of pulse pressure than a similar stroke volume delivered after death? In favor of an affirmative answer one notes that Alexander[20] has found that adrenaline caused increased tone of the intrinsic muscle in the aorta of dogs, and that when this muscle contracted the distensibility of the aorta was increased, a finding which certainly permits the view that aortic distensibility might decrease at death when the muscles relaxed and let the aortic wall expand until it rested on the less vital elastic fibers.

The decisive experiment on this point, made to permit one to compare the pulse wave velocity of a single subject in health and after death, would be obviously very difficult to accomplish, and one doubts whether a comparison made between this velocity during one's last illness and after death would give a conclusive answer. But the less direct evidence does not support the view that the changes occurring at death have a noteworthy effect on the pressure-flow relationship. The reasons for this belief are: First, the changes in elasticity on death, if any are present, seem to be small; for the pulse wave velocity of our cadavers is of the order of magnitude expected in patients of similar age tested during life; thus while a small change at death might well have been missed, a large change in pulse wave velocity would have surely been detected. Second, and more important, threefold, indeed, almost fourfold changes in the distensibility of the compression chamber, as measured by pulse wave velocity, changes much greater than could have occurred at death without our detecting them, were produced experimentally in our cadavers without any important interference with the pressure-flow relationship. Third, when volunteers were bled in the experiments of Warren and co-workers,[4] one must believe that vasoconstriction occurred, but the correlation between the cardiac output estimates made by the Fick method and those made from blood pressure remained excellent. And lastly, adrenaline given in experiments on man, while producing marked changes in blood pressure, caused similar increments in the estimates of cardiac output both from blood pressure and from ethyl iodide methods.[15] Apparently, therefore, either vital phenomena such as vasoconstriction have less effect on the relationship between flow and pressure in the great vessels than has been ordinarily believed, or this effect, by causing a change of diastolic pressure, is compensated by the resulting change in the term for diastolic pressure in our equations. We certainly have not discovered any reason for believing that the blood pressure method of estimating cardiac output will not work as well in living subjects as it does on the cadavers.

Having given the basis for our viewpoint, let us now enquire concerning the evidence for the accuracy of other cardiac output procedures, confining our attention chiefly to the Fick method, because it is thought of by many as providing a standard by which other methods should be judged.

Most authors in discussing the "accuracy" of the Fick method in their hands have had the deviation of the duplicate estimates in mind, and knowledge of the scatter of these,

while of the greatest importance to the proper interpretation of changes in the measurements, is not to be compared with the knowledge of absolute accuracy permitted by our cadaver experiments. Thus McMichael's estimate[21] of an accuracy of 6 per cent is based on the standard error calculated from the deviations found in 100 consecutive cardiac output determinations, in which paired samples of venous blood were taken from the right auricle or right ventricle, within five minutes of one another, and simultaneous duplicate estimations of oxygen uptake were made, while the subjects were in a steady state.[22] In these experiments, where subjects were normal, a fixed 95 per cent arterial oxygen saturation was assumed, and in patients only one sample of arterial blood was taken, so the errors of these estimates are not included in the scatter of the duplicates.[22] Duplicating the arterial blood samples as well as the other items, Donald and co-workers[23] got a value of 8.1 per cent for the standard error of estimates made by the Fick method in the supine position.

A value of 9 per cent for "accuracy" has been based on the data of Harvey and associates[23] and was derived from the limiting values of the range of a small series of duplicate estimations, a far less useful statistic. At a symposium on recent advances in cardiovascular physiology and surgery, held in September, 1953, under the auspices of the Minnesota Heart Association, those present seemed to agree that the accuracy of the Fick method as applied to man should be rated at approximately 15 per cent or 20 per cent, this value meaning simply that when one estimate differed from another by less than this amount the difference should not be regarded as significant, but the exact means of arriving at the figure, and the level at which significance was placed, were not clearly defined. In any event it should be emphasized that all these studies on "accuracy" are in reality studies on consistency of performance, and that they contribute nothing towards an explanation of the difference in level of cardiac output as estimated by the Fick method and by our formulas. Indeed, if one is to judge solely by such tests, I am tempted to point out that, in the data of Cathcart and colleagues,[8] the "accuracy" of cardiac output estimates from blood pressure might be judged greater than that of the Fick method, for the test-retest correlation coefficient of the former is larger but, to tell the truth, the difference is too small to be significant.

The lack of satisfactory data concerning absolute accuracy of the Fick method in man has led to the search for this information in animal experiments, and the first investigation to furnish data from which this information could be obtained, that of Bohr and Henriques,[25] deserves mention for its historical interest. The methods available in 1897 would be considered crude today, and while the average of the Fick estimates was high in comparison with measurements made by a mechanical flowmeter, the individual results scattered widely.

It was not until 1950 that this difficult experiment was repeated by modern methods, and in that year Seely, Nerlick and Gregg[26] compared estimates of cardiac output made by the Fick method with measurements made by a rotameter placed in the pulmonary artery of anesthetized dogs with the chest open. Such experiments are of great technical difficulty, and it should occasion no surprise that, of the 40 experiments started, only 20 were completed; and in only 12 of these were the results considered reliable. Calculating the coefficient of variation from the data of the 12 best experiments, one gets a value of 7 per cent; obviously, the agreement between results secured by the two methods was excellent. However, one is concerned that the results of only 12 of the 20 completed experiments were accepted, and we seriously question whether a better estimate of the accuracy usually secured in the clinic would not be obtained by including at least some of the other results, for some were discarded because of the detection of a type of error—duplicate estimations of oxygen in arterial blood failed to agree—which would pass unnoticed in the great bulk of the clinical work reported, for duplicates have seldom been taken.

In the same year, a somewhat larger series of

comparisons, 36 tests in 10 dogs, were reported by Huggins, Smith and Sinclair.[27] In these experiments Fick estimates could be compared with measurements of cardiac input made by placing a rotameter in the great veins, and the coefficient of variation was 13 per cent, but a reasonable allowance for the coronary circulation, missed by the rotameter, would reduce this value.

Obviously, one has no assurance that an estimate of the accuracy of any methods made in animals under special experimental conditions will apply exactly when the method is used under the great variety of conditions existing in clinical work. Indeed, by using an anesthetized animal to compare results secured by the Fick and those obtained by a mechanical method, one has avoided a difficulty that in the clinic may well be a major source of error, the hazard that the arduous nature of the experiment will of itself alter the cardiac output in a manner varying with the temperament of each subject, so that the results secured will be but a poor measure of the state of the circulation characteristic of the clinical situation in which one is interested.

Therefore, to the author the distance from an anesthetized, open chested dog, subjected to a long and difficult operative procedure, to a living man is a long one. In the early days of cardiac output work, methods which gave results agreeing with the Fick estimates in animal experiments sometimes yielded very different results when applied to man; it was this finding that inclined me away from using the Fick method in animal experiments as a standard by which to judge methods designed for application to man. But technical perfection in animal experiments has increased since that time, and it may be further increased in the future until the difficulties are altogether overcome. The fact is that the two methods of attack, both starting from accurate measurements of cardiac output, the one made in anesthetized dogs, and the other in cadavers, once more have not yielded similar results when applied to man, and the reason for this discrepancy is by no means certain. For those convinced of the absolute accuracy of the Fick results, as the method is performed at present in man, I have supplied the regression equations given in tables 1 and 2 by which one would convert the blood pressure results to the level of the Fick results.

But the author will not advise this conversion on the basis of the present evidence. The results of the new blood pressure method agree too well with those of the older group of methods as to the general level of the cardiac output of resting subjects. Indeed, the correlation of the results secured by the blood pressure method with those of the acetylene and nitrous oxide methods in a variety of conditions is suprisingly good. The author's own ethyl iodide method plainly does not come out so well; the averages agree closely with those of estimates of cardiac output from blood pressure; the difference between the mean stroke volume estimated in 34 healthy persons at rest by both methods is only 2.8 cc., but the difference between the two estimates in many persons is large. Fortunately, in drawing conclusions from results secured by the ethyl iodide method in the past, it was the statistical analyses of the data that were stressed, so proper allowance was made for this variability and the conclusions concerning the major changes in cardiac output to be found in clinical conditions have been largely supported by later work. But it was obviously no mistake to abandon the ethyl iodide procedure 18 years ago.

The average level of basal cardiac output found in healthy young adults by these older methods was about 4 liters per minute, but in similar subjects the Fick method with cardiac catheterization gives greater values, about 6 liters per minute. The reason for this discrepancy has been debated, those partial to the older methods contending it was the excitement inherent in venous and arterial puncture, and in the catheterization, that caused the difference, while the adherents of the Fick method deny this, citing the basal levels of pulse rate and metabolic rate that they so often secure despite the rigors of their method, and they attribute the discrepancy to errors in the design of the older methods. My own opinion is that excitement plays more part than some authors are willing to admit, but I fully

concede that there may well be other factors still unidentified.

However, the unexplained differences in level are not likely to be of great practical importance, for the utility of any method in the clinic lies in its ability to detect differences, to make distinction between the amount of the circulation in health and disease, and to distinguish various clinical and physiologic states from one another. In such tests the blood pressure method has come out well; certainly its ability to detect changes in cardiac output such as those occurring during exercise, after adrenaline and hemorrhage, during fever and anoxemia, and in thyrotoxicosis is evident from the data given in the figures. The important question is, will it make such distinctions as well as the more elaborate methods? And let us not forget that a simple method might make such distinctions with greater accuracy, for the elaborateness of a method, far from guaranteeing its accuracy, introduces errors at every step, and any procedure which may disturb the subject inserts an unpredictable disturbing factor into the results.

In a few instances described in this paper the more elaborate cardiac output methods yielded results differing markedly from those calculated from the blood pressure. Certainly the elaborate methods are subject to the errors inherent in several analyses and measurements of volume and, all but the dye method, also to errors due to leakage from masks, tubing and containers of the gases respired; so an occasional aberrant result is to be expected solely from the effect of chance on the cumulation of these errors. Common experience with the estimation of basal metabolic rates in the clinic illustrates well one source of error, for in the Fick, acetylene and nitrous oxide methods an estimation of metabolic rate is an integral part of the estimation of cardiac output, and the error of the latter estimate cannot be less than the errors occurring in the former. In the absence of duplicate estimations many errors are likely to escape detection. So it is not surprising that, when results obtained by elaborate methods have deviated markedly from those secured by the blood pressure method, it has usually been the latter results that were consistent with the rest of the data. So it was the simple method which made the clinical distinctions most consistently.

Another feature of the results deserves comment. In some comparisons in which correlation is good the slope of the regression exceeds one, so that the blood pressure method exhibits smaller increments than the other methods as cardiac output increases. I have no explanation for this, but it should be realized that in the Fick, acetylene and nitrous oxide methods the estimation of cardiac output is derived from the size of the difference between two samples; as the circulation increases this difference becomes smaller, so that as cardiac output increases the normal errors of analysis cause increasingly greater errors in the estimate. But with the blood pressure method the contrary is true, for as stroke volume increases pulse pressure increases also, so the normal errors of estimating blood pressure cause diminishing errors in the estimate as cardiac output increases. Nevertheless, our blood pressure method has not been standardized in the cadavers against such large stroke volumes as may occur in exercise, anoxemia, or after hemorrhage; nor, of course, have results secured by other methods been subjected to such a test.

Therefore, doubt as to the accuracy of other methods of estimating cardiac output has handicapped the search for limitations in our blood pressure method. We were anxious to scrutinize our results, especially in young people and in the presence of high hypertension, but we have little to report at present. In a child, the cardiac output estimated by the ethyl iodide method differed greatly from the result of the estimate from blood pressure and, obviously, the latter method should certainly not be used on children in its present form without further study. In young adults, tested by each of the methods, we note no greater tendency for the blood pressure estimate to deviate from results secured by other cardiac output methods than is the case in persons within the older age range of our cadavers.[1] In the data of Cathcart and associates[8] results secured in two cases of hypertension deviate

from the run of the data, but in other cases the agreement is excellent and the removal of all cases of hypertension from the series does not improve the correlation between blood pressure and Fick estimates. The large body of data on hypertensive patients studied by the ethyl iodide[13] and acetylene methods[27] have been inspected carefully, but the data are too scattered to be of help. So we have as yet found no basis for a conclusion that the estimate of stroke volume from blood pressure was erroneous in subjects with severe hypertension.

However, a significant difference of result does seem to have been present in tilting experiments[6] where the average cardiac output per minute estimated by blood pressure is little changed by tilting, while the Fick results show a consistently smaller output after tilting. Here again results of the blood pressure estimates resemble more closely the results of older than those of more recent work. But this discrepancy raises the question whether it is proper to apply our formulas to data secured from subjects in the upright position, since all the cadaver experiments on which our method is based were conducted in the horizontal position, because there are such marked physiologic differences between the circulation of subjects in the horizontal and vertical positions. But the exercise experiments of Liljestrand and Zander[15] were conducted with the subject upright, riding a bicycle ergometer, and in these the correlation between the two sets of estimates of cardiac output is excellent.

Certainly limitations in a procedure as simple as ours are to be expected, and they should be diligently sought. It is to be hoped that every worker estimating the cardiac output by some other method will take, with all the care of which he is capable, a series of estimations of blood pressure under conditions identical with those in which the other method is employed and utilize the findings to compare results of the two estimates. But such a comparison must be assessed without the preconceived idea that the more elaborate the method the more correct the result.

However, despite our failure to get convincing evidence of the limitations of our method by studying data already in the literature, there are several clinical situations in which there is evidence that the auscultatory method of taking blood pressure leads to erroneous results, and so would lead to erroneous estimates of cardiac output if our formulae were employed. In aortic regurgitation intra-arterial pressures have proved to be poorly estimated by the auscultatory method in two series.[29, 30] In arms of unusual diameter the standard auscultatory method has given erroneous results unless a cuff of suitable breadth was employed.[29] In arrhythmias the blood pressure may vary so that many estimates might be necessary before a satisfactory average could be secured. Any improvement in the standard method of taking blood pressure would improve the cardiac output estimate as well and there is already evidence that, by using the point of disappearance of sounds to indicate diastolic pressure, and our formula number 72,[1] a small gain in accuracy would occur.

Therefore, although it seems proper to expect that limitations to our simple method will be encountered and that improvements will be suggested, it seems obvious that a rough cardiac output method is now available, so simple that it can be applied by any physician with the apparatus he now has, and that its results correlate reasonably well with those secured by the elaborate cardiac output methods in a wide variety of clinical and physiologic conditions.

While it is certainly to be hoped and expected that attempts to develop and employ cardiac output methods of the highest accuracy obtainable will be pursued despite technical difficulties, it is my opinion that the simpler methods such as this one will have a brighter future in the clinic. Now that a means of assessing their accuracy is at hand, one has every reason to believe that our simple method will suffice to measure cardiac output in most clinical conditions with an accuracy commensurate with our present ability to use this knowledge to the advantage of our patients. Indeed, our studies suggest that means are now available to make a rough estimation of cardiac output as a routine part of every examination of the patient, and that

physicians taking the blood pressure routinely can interpret their findings with greater insight into their physiologic meaning.

Conclusion

The simple formulas, relating cardiac stroke volume to pulse pressure, diastolic pressure and age, and derived from results secured in cadaver experiments in which stroke volume could be measured accurately, have been used as the basis for estimations of cardiac output from clinical data already reported in the literature.

Many instances have been found in which the results of estimates of cardiac output by well-known methods could be compared with estimates made by our formulas from blood pressures taken in conjunction with the other tests. A sample of about 400 such comparisons was taken for study, and in these, estimates of cardiac output from the blood pressures could be compared with estimates made by the Fick, dye, acetylene, ethyl iodide and nitrous oxide methods.

The estimation of cardiac output from blood pressure and age gives excellent duplicates in resting subjects, and one gets the impression that the cardiac output is a more stable and consistent physiological function than certain results secured by the Fick method suggest.

Examples have been found in which estimates of cardiac output from blood pressure correlate well with those of other methods in a wide variety of conditions; such as in resting subjects, during exercise, during anoxemia, after hemorrhage, after adrenaline and in thyrotoxicosis. Thus changes in cardiac output resulting from many experiments, or occurring in many clinical situations are as well shown by the blood pressure method as by the other methods.

The level of cardiac output estimated by the blood pressure method is distinctly below that given by Fick and dye methods, but it seems to be identical, or nearly so, with the levels given by the acetylene, nitrous oxide and ethyl iodide methods.

When the estimate of cardiac output from blood pressure diverges widely from that of another method, as occasionally happens, it is usually the estimate from the blood pressure that yields a result more consistent with the rest of the data.

It appears that a rough method of determining cardiac output is available which can be performed by any doctor with the apparatus he now has.

Acknowledgment

I am indebted to Mrs. Anne Littmann for valuable assistance in the calculations made from the data and in the statistical analysis, and to Mrs. Ruth Besser for much aid in the preparation of the manuscript and figures of both this and the preceding paper.

Sumario Español

Las sencillas fórmulas relacionadas a volumen por contracción cardíaca, presión de pulso, presión diastólica y edad, derivadas de resultados obtenidos en experimentos en el cual el volumen por contracción se pudo medir con exactitud, han sido usadas como la base para estimados de producción total cardíaca de datos clínicos ya informados en la literatura.

Muchos casos se han encontrado en los cuales los resultados de estimados de producción total cardíaca por métodos bien conocidos pueden ser comparados con estimados hechos con esta fórmula de la presión arterial tomada en conjunción con las otras pruebas. Un grupo de aproximadamente 400 semejantes comparaciones fué tomado para estudio, y en estas, estimados de producción total cardíaca obtenidos de presiones arteriales pudo ser comparado con estimados hechos por los métodos de Fick, tinte, acetileno, ioduro etílico y óxido nitroso.

El estimado de producción total cardíaca de la presión arterial y la edad produce excelentes duplicados en sujetos durante el descanso, y uno obtiene la impresión que la producción cardíaca total es una función fisiológica más estable y consistente que ciertos de los resultados obtenidos por el método de Fick sugiere.

Ejemplos han sido encontrados en los cuales estimados de producción cardíaca total de la presión arterial correlacionan bien con aquellos por otros métodos en una variedad extensa de condiciones; como en sujetos durante el descanso, durante el ejercicio, durante la anoxemia, después de hemorragia, luego de la administración de adrenalina y en la tirotoxicosis. De

manera que cambios en producción total cardíaca resultado de muchos experimentos, y ocurriendo en muchas situaciones clínicas son tan bien demostrados por el método de presión arterial como por otros métodos.

El nivel de producción cardíaca total estimado por el método de presión arterial es distintamente menor que aquel obtenido por el método de Fick y de tinte, pero parece idéntico, o aproximado, a los niveles obtenidos por los métodos de acetileno, óxido nitroso e ioduro etílico.

Cuando el estimado de producción cardíaca total obtenido por el método de presión arterial difiere marcadamente de otro método como ocasionalmente ocurre, es usualmente el estimado por presión arterial el que resulta más consistente con el resto de los datos.

Parece ser que hay un método tosco disponible para la determinación de la producción cardíaca total que puede ser usado por cualquier médico con los aparatos que corrientemente el tiene en el presente.

REFERENCES

[1] Starr, I., Schnabel, T. G., Jr., Askovitz, S. I., and Schild, A.: Studies made by simulating systole at necropsy. IV. On the relation between pulse pressure and cardiac stroke volume, leading to a clinical method of estimating cardiac output from blood pressure and age. Circulation **9:** 648, 1954.

[2] Stead, E. A., Jr., Warren, J. V., Merrill, A. J., and Brannon, E. S.: The cardiac output in male subjects as measured by the technic of right atrial catheterization. Normal values with observations on the effect of anxiety and tilting. J. Clin. Investigation **24:** 326, 1945.

[3] Brannon, E. S., Merrill, A. J., Warren, J. V., and Stead, E. A., Jr.: The cardiac output in patients with chronic anemia as measured by the technic of right atrial catheterization. J. Clin. Investigation **24:** 332, 1945.

[4] Warren, J. V., Brannon, E. S., Stead, E. A., Jr., and Merrill, A. J.: The effect of venesection and pooling of blood in the extremities on right atrial pressure and cardiac output in normal subjects with observations on acute circulatory collapse in three instances. J. Clin. Investigation **24:** 337, 1945.

[5] Hickam, J. B., and Cargill, W. H.: Effect of exercise on cardiac output and pulmonary arterial pressure in normal persons and in patients with cardiovascular disease and pulmonary emphysema. J. Clin. Investigation **27:** 10, 1948.

[6] —, and Pryor, W. W.: Cardiac output in postural hypotension. J. Clin. Investigation **30:** 401, 1951.

[7] deWardener, H. E., Miles, B. E., Lee, G. deJ., Churchill-Davidson, H., Wylie, D., and Sharpey-Schafer, E. P.: Circulatory effects of hemorrhage during prolonged light anesthesia in man. Clin. Sc. **12:** 175, 1953.

[8] Cathcart, R. T., Field, W. V., and Richards, D. W., Jr.: Comparison of cardiac Output determined by the ballistocardiograph. (Nickerson apparatus) and by the direct Fick Method. J. Clin. Investigation **32:** 5, 1953.

[9] Kotte, J. H., Iglauer, A., and McGuire, J.: Measurements of arterial blood pressure in the arm and leg. Am. Heart J. **28:** 476, 1944.

[10] Grollman, A.: Effect of high altitude on the cardiac output and its related functions; an account of experiments conducted on the summit of Pike's Peak, Colorado. Am. J. Physiol. **93:** 19, 1930.

[11] —: The cardiac output of man in health and disease. Baltimore, C. C Thomas 1932.

[12] —: The cardiac output of man during the malaise and pyrexia following the injection of typhoid vaccine. J. Clin. Investigation **8:** 25, 1929.

[13] Starr, I., Collins, L. H., Jr., and Wood, F. C.: Studies of the basal work and output of the heart in clinical conditions. J. Clin. Investigation **12:** 13, 1933.

[14] —, Donal, J. S., Margolies, A., Shaw, R., Collins, L. H., and Gamble, C. J.: Studies of the heart and circulation in disease; estimation of basal cardiac output, metabolism, heart size and blood pressure in 235 subjects. J. Clin. Investigation **13:** 561, 1934.

[15] —, Gamble, C. J., Margolies, A., Donal, J. S., Jr., Joseph, W., and Eagle, E.: A clinical study of the action of 10 commonly used drugs on cardiac output, work and size, on respiration, on metabolic rate, and on the electrocardiogram. J. Clin. Investigation **16:** 799, 1937.

[16] Liljestrand, G., and Zander, E.: Vergleichende Bestimmungen des Minutenvolumens des Herzens beim Menschen mittels der Stickoxydulmethode und durch Blutdruckmessung. Ztschr. ges. exper. Med. **59:** 105, 1928.

[17] Cournand, A., Lequime, J., and Regniers, P.: L'Insuffisance cardiaque chronique, études physio pathologiques. Paris, Masson et Cie, 1952.

[18] Remington, J. W., Hamilton, W. F., and Dow, P.: Some difficulties involved in the prediction of the stroke volume from the pulse wave velocity. Am. J. Physiol. **144:** 536, 1945.

[19] Lawton, R. W.: Personal communication.

[20] Alexander, R. S.: Mechanics of vasoconstriction. Federation Proc. **12:** 3, 1953.

[21] McMichael, J.: Dynamics of Heart Failure. Brit. M. J. **2:** 525, 1952.

[22] —: Personal communication.

[23] DONALD, K. W., BISHOP, J. M., CUMMING, G., AND WADE, O. L.: The effect of nursing positions on the cardiac output in man. Clin. Sc. **12:** 199, 1953.

[24] HARVEY, R. M., FERRER, M. I., CATHCART, R. T., RICHARDS, D. W., JR., AND COURNAND, A.: Some effects of digoxin upon the heart and circulation in man. Digoxin in left ventricular failure. Am. J. Med. **4:** 439, 1949.

[25] BOHR, C., AND HENRIQUES, V.: Recherches experimentales sur la production de l'acide carbonique et la consommation d'oxygene dans le poumon (combustion pulmonaire). Arch. Physiol. Normal et Path. **9:** 604, 1897.

[26] SEELY, R. D., NERLICH, W. E., AND GREGG, D. E.: A comparison of cardiac output determined by the Fick procedure and a direct method using the rotameter. Circulation **1:** 1261, 1950.

[27] HUGGINS, R. A., SMITH, E. L., AND SINCLAIR, M. A.: Comparisons between the cardiac input measured with a rotameter and the output determined by the direct Fick method in open-chested dogs. Am. J. Physiol. **160:** 183, 1950.

[28] SUAREZ, J. R. E.: Et Volumen Minuto Cardiaco. Buenos Aires, Libería y Editorial "El Ateneo," 1950.

[29] RAGAN, C., AND BORDLEY, J., III.: Measurements of Blood Pressure. Bull. Johns Hopkins Hosp. **69:** 526, 1941.

[30] STEELE, J. M.: Measurements of arterial pressure in man. J. Mt. Sinai Hosp. **8:** 1049, 1941–2.

Anticoagulant Therapy in Private Practice

By CHARLES A. L. STEPHENS, JR., M.D.

One hundred eighty-one patients suffering from 216 separate episodes of thromboembolism were treated with anticoagulants by the author in private practice. The indications and contraindications for anticoagulants are described and the results tabulated and analyzed. Practical methods of administration of anticoagulants are discussed. Long-term ambulatory anticoagulant therapy is considered as a special and important aspect of the problem of thromboembolism with the results indicating it to be a practical and feasible form of preventive therapy worthy of more widespread use.

THE DISCOVERY of heparin by McClean in 1916[1] and the identification of bishydroxycoumerin (Dicumarol) by Link and his co-workers in 1934 as the agent responsible for sweet clover disease in cattle,[2] stimulated studies of the clinical use of anticoagulant therapy. The excellent work of Jorpes,[3] Zilliacus,[4] Barker[5, 6] of the Mayo Clinic, and Wright[7, 8] of New York, and others,[9, 10, 11] has crystallized the indications and contraindications and evaluated the benefits and dangers of this form of therapy in thromboembolic disease.

There remain some, however, who question the value of anticoagulant therapy.[12, 13] There are others who maintain that these drugs can be safely and effectively administered only by a few experts supported by a Research Laboratory or a teaching hospital.[14, 15]

During the past six years in private practice in the community of Tucson, Arizona, the author has successfully administered anticoagulant therapy to 181 patients suffering from thromboembolic conditions. It is the purpose of this report to review this experience and to demonstrate that anticoagulant therapy is a practical, feasible and effective form of therapy in private practice in a small community.

METHODS

It was felt that anticoagulant therapy was indicated in any patient who suffered from thromboembolism and in whom one or more of the contraindications listed below did not exist. Heparin and/or Dicumarol was given to patients suffering from those diseases listed in table 1.

Anticoagulant therapy was not administered to patients suffering from one or more of the diseases listed in table 2. Anticoagulant therapy was administered with caution under the conditions listed in table 3.

Selection of the Anticoagulant. Heparin was chosen whenever an immediate anticoagulant effect was desired. Patients with pulmonary embolism or those with thrombophlebitis where pulmonary emboli might be anticipated are examples of need for immediate anticoagulant effect. Heparin was not given to patients suffering from coronary thrombosis with myocardial infarction because: (1) evidence indicates that the first 36 hours after infarction are not attended by a high thromboembolic morbidity or mortality; (2) heparin therapy is of necessity disturbing to a patient who might profit more by rest and supportive measures during the first few days. Dicumarol was chosen as a maintenance anticoagulant in all cases capable of taking oral medication.

Method of Administration. When given, heparin was administered intravenously every four hours. The initial dose was 50 mg. Three hours later a Lee-White coagulation test was performed and on the fourth hour the heparin was again administered intravenously with the exceptions noted below. This was continued around the clock. If the Lee-White coagulation time was below 20 minutes, 75 mg. were given. If it was between 20 and 30 minutes, 50 mg. were given, and if it was between 30 and 45 minutes, 25 mg. were given. If it was above 45 minutes no heparin was administered on the fourth hour.

The difference in patient response was not determined by the heparin tolerance test. Heparin in Pitkins menstruum or Depo-Heparin with or without a vasoconstrictor was not used. The evidence of Barker and his co-workers indicates that absorption of these preparations is too variable to insure either an effective or safe therapeutic level. There are no well controlled studies reported to date indicating the value or safety of intramuscular heparin in a retarding menstruum.

The thermolability of heparin and the variable patient tolerances necessitates the continued use of the Lee-White test. It has been found that different batches of heparin vary in their effect on the same patient, possibly because of exposure to high temperatures in transit. This may be an important factor in warm climates.

TABLE 1.—*Indications for the Use of Anticoagulants*

1. Heart disease with auricular fibrillation and mural thrombi.
2. Coronary occlusion and myocardial infarction.
3. Cerebral thromboses.
4. Peripheral arterial thromboses.
5. Mesenteric thromboses.
6. Arterial embolism.
7. Thrombophlebitis and/or "phlebothrombosis."
8. Pulmonary embolism.
9. Central retinal artery or vein thrombosis.
10. Phlebitis migrans.
11. Buerger's disease with evidence of acute activity.

It has been helpful to both patient and technician to insert a child's spinal needle or a polyethyline tube in a vein in the forearm to facilitate the administration of heparin and the withdrawal of blood for coagulation tests.

Dicumarol was given by mouth. The initial dose was 300 mg. and 24 hours later, 200 mg. were administered. Lesser amounts were used in patients in whom caution was felt to be necessary. (See table 3.) The prothrombin time was determined daily by means of the Link-Shapiro modification of the Quick method[17] and the value desired was two to two and one half times the control. Experience has confirmed the necessity of drawing blood for the prothrombin time just prior to the next due dose of heparin,[18, 11] for heparin will influence the prothrombin time. Heparin was discontinued when the prothrombin time reached an adequate therapeutic level and the patient was then maintained on Dicumarol.

Continuation of Therapy. Anticoagulant therapy was continued as long as the patient exhibited active thromboembolic disease. In instances where the etiology or evidence of the thromboembolic disease persisted, the patient was maintained on anticoagulant therapy in an ambulatory fashion. In no instances was the heparin or Dicumarol discontinued abruptly, but the drug was tapered off over a period of 7 to 10 days.

TABLE 2.—*Contraindications for the Use of Anticoagulants*

1. Duodenal or gastric ulcer.
2. Gastric carcinoma.
3. Subacute bacterial endocarditis.
4. Severe hypertensive disease.
5. Cirrhosis of the liver.
6. Hepatitis.
7. Dissecting aneurysm of the aorta.
8. Preceding a traumatic operation, such as transurethral resection.
9. Vitamin C deficiency.
10. Blood dyscrasias interfering with blood clotting.
11. Late pregnancy.

TABLE 3.—*Conditions Requiring Caution in the Use of Anticoagulants*

1. Hypoprothrombinemia.
2. Acute or chronic passive congestion of the liver (heart failure).
3. Thrombotic thrombocytopenic purpura.
4. Impending delivery or non-traumatic surgery.
5. Renal insufficiency.

In those patients in whom anticoagulant therapy was continued on an ambulatory basis, prothrombin determinations were made once weekly, (rarely once in two weeks), for it was felt that the patient was under better control if the prothrombin time was determined once every seven days. The result of the prothrombin time was recorded on a specially designed form, and the dosages for the following seven days were recorded on this same sheet. The patient was then informed by telephone what his dosage of Dicumarol should be for the coming week.

This method of ambulatory anticoagulant therapy requires very little time or effort on the part either of patient or doctor and has permitted patients on such therapy to lead full and active lives without interference or fatal thromboembolism.

RESULTS

Anticoagulant therapy has been administered for the past six years to 181 patients suffering from thromboembolic disease. Prior to treatment there were 216 thromboembolic episodes in these 181 patients. There were five additional patients who were given anti-

TABLE 4.—*Nature of Thromboembolic Episodes Occurring in 181 Patients*

Disease	No. of Episodes
Thrombophlebitis	88
Coronary thrombosis	55
Pulmonary emboli	16
Auricular fibrillation with intra-auricular thrombosis	12
Cerebral thrombosis	11
Peripheral arterial occlusion	10
Peripheral emboli	9
Buerger's disease	6
Central retinal vein thrombosis	3
Mesenteric thrombosis	2
Phlebitis migrans	1
Polycythemia	1
Multiple sclerosis (experimental)	2
Prevent thrombosis	5
	221

TABLE 5.—*Major Hemorrhage*

Type of Bleeding	No. of Cases
(a) Gross hematuria	7
(b) Gross melena	2 (due to diverticulae)
(c) Hematemesis	1 (due to gastric cancer)
(d) Cerebral hemorrhage	1
(e) Hemorrhage in wall of coronary	1
	12 (7 per cent)

TABLE 7.—*Mortality While on Anticoagulants*

Disease	No. of Cases
Cancer	2
*Heart failure	6
Collagen disease	1
Cerebral hemorrhage	1
	10

* All were examined post mortem and there was no further thromboembolism present.

coagulant therapy to prevent thromboembolism.

There were 105 males and 76 females. The age of the patients varied from 16 years to 88 years.

The distribution of the pretherapy thromboembolic episodes is shown in table 4. Heparin was administered as an initial anticoagulant to 96 cases (53 per cent) and all received Dicumarol therapy. (See table 4.)

Hemorrhage

Of the 181 patients given anticoagulant therapy major bleeding occurred in 12 patients (7 per cent). (See table 5.) Minor bleeding occurred in 36 patients (20 per cent). (See table 6.)

Two deaths could possibly be attributed to Dicumarol therapy. The first occurred in a 72 year old white woman who suffered from cerebral arteriosclerosis and multiple cerebral thrombi and who died of a cerebral hemorrhage. The second death occurred in a 69 year old white man who suffered from a coronary thrombosis with posterior myocardial infarction and while on adequate anticoagulant treatment suffered another myocardial infarction one week later. At postmortem examination hemorrhage into the wall of the anterior descending coronary artery was found. Such phenomena are, however, frequently encountered in patients not on anticoagulants.

The maximum over-all mortality from hemorrhage due to anticoagulants might therefore be considered to be 0.11 per cent. All bleeding occurred in patients receiving Dicumarol; there were no episodes of hemorrhage while on heparin.

Therapy of Hemorrhage. Cessation of anticoagulant therapy constituted the major form of treatment of bleeding due to anticoagulants. In four instances vitamin K (recently K_1 oxide) was given and in only one case was whole blood transfusion a necessary addition. Because no bleeding occurred as a result of heparin therapy protamin was not used.

Thromboembolism

There were two episodes of new thromboembolism while on anticoagulant therapy (0.11 per cent). The first of these was in a woman with auricular fibrillation and probable mural thrombus with a previous history of multiple peripheral emboli who had one embolus to the right leg eight days after anticoagulant treatment was started. No further emboli have occurred in this patient

TABLE 6.—*Minor Bleeding*

Type of Bleeding	No. of Cases
(a) Microscopic hematuria	12
(b) Petechiae and ecchymoses	7
(c) Bleeding gums	6
(d) Soft tissue hematomata	7
(e) Epistaxis	4
	36 (20%)

TABLE 8.—*Reasons for Discontinuing Anticoagulants*

Stopped on advice	4
Stopped against advice	7
Changed locale—facilities unavailable	2
Continued at home	2
Stopped because of bleeding	2
	17

after five and one-half years of continuous therapy on an ambulatory basis.

The second was an elderly white man with polycythemia rubra and multiple episodes of venous thrombosis; four days after starting treatment with heparin and Dicumarol and two days after discontinuing heparin therapy acute thrombophlebitis developed in a lower extremity. The prothrombin time at the time of onset was 39 seconds with a control of 15 seconds. Continuation of treatment with Dicumarol led to subsidence of the thrombotic episode.

Ambulatory Anticoagulant Therapy

Fifty-three patients were continued on long term anticoagulant therapy for a total of 15,507 days of therapy. This averages 293 days per patient. The range was from 38 days to 2,045 days. Of this group 10 died of causes unassociated with thromboembolic phenomena while on therapy. (see Table 7.)

The remaining cases (43 patients) continued anticoagulant therapy for variable periods of time. Therapy was eventually discontinued in 15 of the cases for the reasons listed in table 8, and two of this group continued anticoagulant therapy at home under the care of their local physicians. Twenty-six of this group are currently still on ambulatory anticoagulant therapy without untoward episodes of either bleeding or thromboembolism.

Of the seven patients who stopped anticoagulant therapy against advice, five died thereafter of thromboembolism; two remain alive and well two and four years respectively, after discontinuing treatment. (See table 8.)

Comments

No statistically valid conclusions can be drawn from the data in this study other than the observation that anticoagulant therapy can be safely and effectively administered in private practice. The incidence of thromboembolism while on therapy of 0.11 per cent and the incidence of major hemorrhage (7 per cent) are not in excess of and, in most instances, are below the complications reported in other studies.[9]

The effectiveness of the procedure can only be implied from the numbers of cases here reported. Short-term therapy has been well substantiated by larger controlled studies by others.[19, 20] Ideally, long-term ambulatory anticoagulant therapy should be evaluated by similar controlled and statistically valid studies. This presents great practical difficulties. However, it should be pointed out that out of seven of our patients who discontinued therapy against advice, five are dead of thromboembolism in contrast to an incidence of fatal thromboembolism in those who continued therapy of 0 per cent.

The experience of the author confirms that of others that ambulatory anticoagulant therapy properly applied is a life-preserving measure.

Conclusions

1. Acute and chronic thromboembolic conditions can be successfully treated with anticoagulants in private practice with a reasonable conscientious effort on the part of the patient and his physician.

2. This can be carried out satisfactorily in private practice in a small community provided that: (a) there are laboratory facilities capable of producing accurate prothrombin determinations; (b) the physician will assume the responsibility inherent in this form of therapy.

3. The incidence of complications in this series agreed favorably with those reported from teaching hospitals and research laboratories.

4. The results of this and other studies warrant more extensive investigation and use of ambulatory anticoagulant therapy.

Sumario Español

Ciento ochento y uno pacientes sufriendo con 216 episodios diferentes de tromboembolismo fueron tratados con anticoagulantes por el autor en su práctica privada. Las indicaciones y contraindicaciones para el uso de anticoagulantes se describen y los resultados se tabulan y se analizan. Métodos prácticos para la administración de los anticoagulantes se discuten. La terapia ambulatoria con anticoagulantes a término prolongado se considera como un aspecto especial e importante en el

problema del tromboembolismo con resultados que indican ser una forma práctica y factible de terapia preventiva meritoria de uso más extenso.

REFERENCES

[1] McLean, J.: The thromboplastic action of cephalin. Am. J. Physiol. **41:** 250, 1916.

[2] Link, K. P.: The anticoagulant from spoiled clover. Hay-Harvey Lectures **39:** 162, 1943.

[3] Jorpes, E.: Heparin. Oxford Medical Publications. 1939.

[4] Zilliacus, H.: On the specific treatment of thrombosis and pulmonary embolism with anticoagulants, with particular reference to the post thrombotic sequelae. Acta med. scandinav. Suppl. 171: 1, 1946.

[5] Barker, N. W., Nygaard, K. K., Walters, W., and Priestley, J. T.: A statistical study of postoperative venous thrombosis and pulmonary embolism. I, II, III, IV Proc. Staff Meetings, Mayo Clinic **15:** 769, 1940; **16:** 1, 17, 33, 1941.

[6] —, Hines, Edgar A., Kvale, Walter F., and Allen, Edgar V.: Dicumarol—it's action, clinical use and effectiveness as an anticoagulant drug. Am. J. Med. **3:** 634, 1947.

[7] Wright, I. S., and Foley, W. T.: Use of anticoagulants in the treatment of heart disease, Am. J. Med. **3:** 718, 1947.

[8] —: The Pathogenesis and Treatment of Thrombosis. New York, Grune and Stratton, 1952.

[9] Nichol, E. S.: The risk of hemorrhage in anticoagulant therapy. Ann. Western Med. & Surg. **4:** 71, 1950.

[10] Allen, R. W.: The clinical use of anticoagulants. Report of treatment with Dicumarol in 1686 postoperative cases. J.A.M.A. **134:** 323, 1947.

[11] Marple, C., and Wright, I. S.: Thromboembolic Conditions and Their Treatment with Anticoagulants. Springfield, Ill., Charles C Thomas, 1950.

[12] Schnur, S.: Mortality and other studies questioning the evidence for and value of routine anticoagulant therapy in acute myocardial infarction. Circulation **7:** 855, 1953.

[13] De Takats, G.: Anticoagulant therapy in surgery. J.A.M.A. **142:** 527, 1950.

[14] Russek, H. I., and Zohman, B. L.: Anticlotting therapy for myocardial infarction. Am. J. M. Sc. **225:** 8, 1953.

[15] Baer, S., Heine, W. I., and Krasnoff, S. O.: The mortality of acute myocardial infarction in private practice. Am. J. M. Sc. **222:** 500, 1951.

[16] Hauch, E. M. and Barker, N. W.: Experiences with heparin: comparative effects of intravenous and subcutaneous administration in the same individuals. J. Lab. & Clin. Med. **38:** 550, 1951.

[17] Shapiro, S.: Hyperprothrombinemia: premonitory sign of thromboembolization. (description of technic). Exper. Med. & Surg. **2:** 103, 1944.

[18] Long, H., Hurn, M., and Barker, N. W.: Effect of heparin on the prothrombin time. Proc. Staff Meet., Mayo Clin. **21:** 225, 1946.

[19] Wright, I. S., Marple, C. D., and Beck, D. F.: Anticoagulant therapy of coronary thrombosis with myocardial infarction. J.A.M.A. **138:** 1074, 1948.

[20] —, —, and —: Report of Committee for Evaluation of Coronary Thrombosis with Myocardial Infarction. (Progress report on statistical analysis of first 800 cases studied by this committee.) Am. Heart J. **36:** 801, 1948.

Studies on the Renal Circulation and Renal Function in Mitral Valvular Disease

I. Effect of Exercise

By Lars Werkö, M.D., Edvardas Varnauskas, M.D., Harald Eliasch, M.D., Jan Ek, M.D., Härje Bucht, M.D., Bengt Thomasson, M.D., and Jonas Bergström, M. K.

In 31 patients with mitral stenosis of varying severity the effect of light, steady exercise during 15 to 17 minutes on renal function and renal circulation has been studied during heart catheterization. The results have been compared with the values obtained at rest in 72 patients with mitral stenosis. Exercise produced a decrease in clearance of para-aminohippurate and sodium excretion and an increase in renal resistance, changes not produced in normal individuals. Cardiac output and pulmonary pressures increased. In patients with right heart failure exercise produced increased pressures but no increase in cardiac output, and only slight changes in clearance but increase in renal resistance and renal venous pressure.

DURING the last decade, renal function in heart disease has been subject to intense research. The occurrence of renal changes in congestive heart failure has been repeatedly demonstrated and its importance debated[1, 13, 19, 20, 25-27, 30] Decreased cardiac output or elevated venous pressure have been suggested as possible causative factors but no conclusions have been reached. It had been shown earlier that there is a marked decrease of renal blood flow in cases with mitral valvular disease[34] (without elevation of right auricular pressure), a change similar to that found in cases with right heart failure.

The present investigation constitutes an attempt to correlate changes in renal blood flow, glomerular filtration rate and sodium excretion with changes in cardiac output and blood pressures in a large series of patients with mitral valvular disease studied at rest and during exercise.

Material

The subjects studied were 72 patients considered, on clinical and radiologic evidence, to have rheumatic mitral valvular disease. They were divided in four functional groups.[12] Selection was random. Patients with complicating aortic stenosis were excluded, but not patients with elevated arterial blood pressure. Some of the patients in groups III and IV had signs of right heart failure, with elevated right auricular pressure.

No patient had any record of renal disease, and, in all cases without right heart failure, the urine was free from protein and had a normal sediment.

Methods

All patients were studied in the morning, recumbent, and in the postabsorptive state. An indwelling catheter was placed in the urinary bladder. Para-aminohippurate (PAH) was given intramuscularly according to the method of Bucht[8, 9] and inulin intravenously, at the start of the procedure.

The pulmonary artery was catheterized according to the technic of Cournand and Ranges[11, 22, 23] and an indwelling arterial needle placed in the brachial artery. Subsequently the bladder was emptied and the first urine collection period started. Every 15 to 17 minutes the bladder was again emptied and rinsed twice with distilled water and air. Simultaneously a blood sample for clearance determination was taken from the arterial needle.

About 30 minutes after the heart catheter had been placed in the pulmonary artery, the first resting cardiac output was determined by the Fick method, with simultaneous sampling of blood from the brachial and pulmonary arteries and collection of expired air. Immediately afterward the blood pressures in the pulmonary artery and brachial artery, and the pulmonary capillary venous pressure[23] were registered with the Tybjaerg-Hansen[32] electrical manometer. In some cases the right auric-

From the IVth Medical Service and Central Laboratory, St. Erik's Hospital, Stockholm, Sweden.

Aided by grants from the Swedish Medical Research Council and the Wallenberg Foundation.

TABLE 1.—*Results in 26 Cases of Mitral Stenosis Belonging to Group I–II. Rest*

a

	BSA M.²	Age	Heart vol. ml./M.²	Art. O_2 satur. %	Pulse rate	Pressure mm. Hg				Vascular resistance dyne sec. cm.$^{-5}$	
						Pulm. art. mean	PCV mean	Brach. art. mean	R. aur. mean	Pulm.	System.
n	26	26	26	21	26	26	26	25	24	25	25
Mean	1.66	35.7	512	93.2	79.6	19.9	12.9	90.9	1.13	97.1	1259
S.E.			29.0	0.50	3.35	1.08	1.13	3.02	0.43	19.4	89
S.D.			148	2.25	17.1	5.52	5.78	15.1	2.09	40.3	444

b

	A-V O_2 diff. ml./L.	Card. ind. L./min./M.²	Clearance ml./min./1.73 M.² BSA		FF %	RBF ml./1.73 M.² BSA	RBF % of CO	Renal resist. dyne sec. cm.$^{-5}$	Hematocrit	T mean sec.	TPV L./1.73 M.² BSA
			Inulin	PAH							
n	26	25	26	26	26	25	25	25	25	24	25
Mean	40.5	3.59	108.7	404.8	27.8	731.0	12.2	105.6	38.5	11.9	3.05
S.E.	2.26	0.21	6.31	25.9	1.07	43.4	0.68	5.8		0.74	0.11
S.D.	11.5	1.03	32.2	132	5.48	216.8	3.4	29.0		3.61	0.55

ular pressure was registered simultaneously through a second catheter; in the remaining cases the right auricular pressure was registered when the catheter was introduced.

When the pressures had been registered the bladder was rapidly emptied. During the following 15 to 17 minutes the patient performed exercise equaling about 70 kilogrammeters per minute by pedaling a cycle ergometer after the method of Eliasch and co-workers.[14, 15, 16] The blood pressures were repeatedly registered and the cardiac output again determined after 10 to 12 minutes of work.

Immediately after cessation of exercise the bladder was again emptied and samples taken. In some cases another set of values was obtained after the subject had rested for 15 to 20 minutes. The technics are reported in detail earlier.[14, 15, 16, 22, 23]

In two cases one catheter was placed in the pulmonary artery and another in the right renal vein.[33] Renal venous blood was sampled simultaneously with arterial blood and analyzed for para-aminohippurate. The renal extraction of para-aminohippurate was calculated in per cent from the concentrations in the arterial and renal venous blood.

RESULTS

Table 1, *a* and *b*, contains the resting values obtained in the 26 cases in group I and II. The

TABLE 2.—*Results in 32 Cases of Mitral Stenosis Belonging to Group III. Rest*

a

	BSA M.²	Age	Heart volume ml./M.²	Art. O_2 saturation %	Pulse Rate	Pressure mm. Hg				Vascul. resist. dyne sec. cm.$^{-5}$	
						Pulm. art. mean	PCV mean	Brach. art. mean	R. aur. mean	Pulm.	System.
n	32	32	32	32	32	32	32	32	32	32	32
Mean	1.62	42.4	609	92.2	82.4	37.5	21.3	93.8	1.91	308	1670
S.E.			28.3	0.53	3.36	2.88	0.89	3.04	0.31	50.1	82.9
S.D.			160	2.97	19.0	16.3	5.81	17.2	1.76	283	469

b

	A-V O_2 diff. ml./L.	Card. ind. L./min./M.²	Clearance ml./min./1.73 M.² BSA		FF %	RBF ml./1.73 M.² BSA	RBF % of CO	Renal resist. dyne sec. cm.$^{-5}$	Hematocrit	T mean sec.	TPV L./1.73 M.² BSA
			Inulin	PAH							
n	32	32	31	32	31	32	26	32	32	30	32
Mean	51.2	2.67	99.5	322.5	31.0	586.1	12.8	136.4	38.1	15.1	2.91
S.E.	1.75	0.35	4.97	15.5	1.03	28.1	0.68	8.61		0.93	0.094
S.D.	9.95	1.98	27.7	87.6	5.74	163	3.49	48.7		5.11	0.53

TABLE 3.—*Results in Seven Cases of Mitral Stenosis Belonging to Group IV. No right heart failure. Rest*

a

	BSA M.²	Age	Heart volume ml./M.²	Art. O_2 saturation %	Pulse Rate	Pressure mm. Hg				Vascular resist. dyne sec. cm.$^{-5}$	
						Pulm. art. mean	PCV mean	Brach. art. mean	R. aur. mean	Pulm.	System.
n	7	7	7	6	7	7	7	6	7	7	6
Mean	1.62	50.1	796	82.8	97.4	52.6	24.0	97.7	1.6	597	2245
S.E.			127	6.14	8.73	7.48	2.12	6.66		119	301
S.D.			336	2.51	23.1	19.8	5.60	16.7		314	736

b

	A-V O_2 diff. ml./L.	Card. ind. L./min. /m.²	Clearance ml./min./1.73 M.² BSA		FF %	RBF ml./1.73 M.² BSA	RBF % of CO	Renal resist. dyne sec. cm.$^{-5}$	Hemato-crit	T mean sec.	TPV L./1.73 M.² BSA
			Inulin	PAH							
n	7	7	7	7	7	6	6	5	6	6	6
Mean	65.7	2.11	76.3	216.4	34.9	398.0	10.8	183.0	38.7	17.80	3.89
S.E.	3.17	0.20	8.43	14.5	2.60	23.5	1.30	17.4		2.06	0.33
S D.	8.38	0.53	22.3	38.4	6.87	57.6	3.18	38.8		5.04	0.80

mean heart volume for these groups was 512 ml. per square meter of body surface area. The pressure in the pulmonary artery was 19.9 mm. Hg, the pulmonary capillary venous pressure, 12.9 mm. Hg and the right auricular pressure 1.13 mm. Hg. The mean cardiac index for the group was 3.59 liters per minute per square meter of body surface. The renal clearance of inulin was 108.7 ml. per minute, of para-aminohippurate, 404.8 ml. per minute, with a filtration fraction of 27.8 per cent. The renal fraction of the cardiac output was 12.2 per cent. The total plasma volume was 3.05 liters. The thoracic mean circulation time was 11.9 seconds.

Table 2, *a* and *b*, contains the same values obtained in the 32 cases in group III. The mean heart volume was 609 ml. per square meter of body surface. The pressure in the pulmonary artery was 38.2 mm. Hg, the pulmonary capillary venous pressure, 21.9 mm. Hg and the right auricular pressure, 2.12 mm. Hg. The mean cardiac index for the group was 2.64 liters per minute per square meter of surface area.

TABLE 4.—*Results in Seven Cases of Mitral Stenosis Belonging to Group IV. Right Heart Failure. Rest*

a

	BSA M.²	Age	Heart vol. ml./M.²	Art. O_2 satur. %	Pulse rate	Pressure mm. Hg				Vascular resist. dyne sec. cm.$^{-5}$	
						Pulm. art. mean	PCV mean	Brach. art. mean	R. aur. mean	Pulm.	System.
n	7	7	6	6	7	7	7	7	7	7	7
Mean	1.73	42.6	807	90.4	75.1	68.3	26.4	96.3	9.1	1076	2146
S.E.			133	1.68	5.93	6.16	2.38	8.20	1.20	203	212
S.D.			296	4.12	15.7	16.3	6.29	21.7	3.19	538	560

b

	A-V O_2 diff. ml./L.	Card. ind. L./min. /m.²	Clearance ml./min./1.73 M.² BSA		FF %	RBF ml./1.73 M.² BSA	RBF % of CO	Renal resist. dyne sec. cm.$^{-5}$	Hemato-crit	T mean sec.	TPV L./1.73 M.² BSA
			Inulin	PAH							
n	7	7	7	7	7	7	7	7	7	7	7
Mean	72.4	1.94	83.0	204.6	43.3	403.6	11.2	199.7	43.4	23.7	3.96
S.E.	4.31	0.17	10.6	38.8	4.11	77.4	1.64	26.8		3.27	0.23
S.D.	11.4	0.46	28.1	102.7	10.9	204.8	4.33	70.9		8.66	0.61

TABLE 5. *Results in 15 Cases of Mitral Stenosis Belonging to Group I–II. Rest and Exercise*

	Art. O_2 satur. %	Pulse rate	Pressure mm. Hg				Vascular resistance dyne sec. cm.$^{-5}$		A-V O_2 diff. ml./L.	Card. ind. L./min./M.^{2}	Clearance ml./min./1.73 M.^{2}		FF %	RBF ml./1.73 M.^{2} BSA	RBF % of CO	Renal resist dyne sec. cm.$^{-2}$	Na^+ μEq./min.
			Pulm. art. mean	PCV mean	Brach. art. mean	R. aur. mean	Pulm.	System.			Inulin	PAH					
n	14	15	15	14	15	14	14	15	15	15	15	15	15	15	15	15	15
Mean diff.	−0.55	18.2	8.1	7.4	6.2	0.33	−1.9	−175	24.7	0.7	−2.5	−48.5	3.1	−90	−3.46	22.9	−38.8
S.E. diff.	0.34	3.49	1.64	1.51	2.63		9.19	66.9	2.14	0.20	6.95	15.4	0.97	29.2	0.76	5.60	12.3
S.D. diff.	1.29	13.5	6.36	5.65	10.2		34.4	259	8.27	0.77	26.9	59.7	3.77	113	2.95	21.7	47.5
t	1.62	5.21	4.94	4.90	2.36		<1	2.61	11.5	3.5	<1	3.15	3.20	3.08	4.55	4.08	3.15
p	>0.05	<0.001	<0.001	<0.001	0.05–0.01			0.05–0.01	<0.001	0.01–0.001	0.7	0.01–0.001	0.01–0.001	0.01–0.001	<0.001	0.01–0.001	0.01–0.001

TABLE 6.—*Results in Nine Cases of Mitral Stenosis Belonging to Group III–IV. No Right Heart Failure. Rest and Exercise*

	Art. O_2 saturation %	Pulse rate	Pressure mm. Hg				Vascular resistance dyne sec. cm.$^{-5}$		A-V O_2 diff. ml./L.	Card. ind. L./min./m.^{2}	Clearance ml./min./1.73 M.^{2}		FF %	RBF ml./1.73 M.^{2} BSA	RBF % of CO	Renal resistance dyne sec. cm.$^{-2}$	Na^+ μEq./min.
			Pulm. art. mean	PCV mean	Brach. art. mean	R. aur. mean	Pulm.	System.			Inulin	PAH					
n	8	9	9	9	6	9	9	6	9	9	8	9	8	9	9	6	9
Mean diff.	0.48	32.0	21.4	12.0	10.2	0.77	87.1	−160	32.9	0.86	−4.0	−36.8	3.4	−71.0	−3.38	24.8	−46.9
S.E. diff.	0.63	3.33	2.30	2.64	2.33		53.0	74.7	4.10	0.19	4.9	13.8	0.96	23.8	0.69	4.98	14.5
S.D. diff.	1.77	10.0	6.91	7.92	5.71		159	183	12.3	0.58	14.0	41.3	2.72	71.3	2.07	12.2	43.6
t	<1	9.61	9.30	4.54	4.38		1.64	2.14	8.02	3.51	0.8	2.67	3.54	2.98	4.90	4.98	3.23
p		<0.001	<0.001	0.01–0.001	0.01–0.001		>0.05	>0.05	<0.001	0.01–0.001	>0.05	0.05–0.01	0.01–0.001	0.05–0.01	<0.001	<0.001	0.01

TABLE 7.—*Results in Seven Cases of Mitral Stenosis Belonging to Group III–IV. Right Heart Failure. Rest and Exercise*

	Art. O_2 satur.	Pulse rate	Pressure mm. Hg				Vascular resistance dyne sec. cm.$^{-5}$		A-V O_2 diff. ml./L.	Card. ind. L./min./m.^{2}	Clearance ml./min./1.73 M.^{2}		FF %	RBF ml./1.73 M.^{2} BSA	RBF % of CO	Renal resistance dyne sec. cm.$^{-2}$	Na^+ μEq./min.
			Pulm. art. mean	PCV mean	Brach. art. mean	R. aur. mean	Pulm.	System.			Inulin	PAH					
n	5	7	6	7	7	7	6	7	7	7	7	7	7	7	7	7	7
Mean diff.	0.02	33.0	24.3	7.9	5.4	4.7	286	−23.0	36.6	0.26	−8.0	−23.7	2.6	−48.0	−1.79	65.7	−52.1
S.E. diff.	0.21	6.84	6.04	1.99	1.33	0.75	328	26.2	8.35	0.28	5.78	15.2	1.49	30.3	1.27	52.5	16.1
S.D. diff.	0.48	18.1	13.5	5.27	3.51	1.98	803	69.4	22.1	0.75	15.3	40.1	3.95	80.2	3.35	139	42.7
t	<1	4.82	4.02	3.97	4.06	6.27	<1	<1	4.38	<1	1.38	1.56	1.74	1.58	1.41	1.25	3.24
p		0.01–0.001	0.05–0.001	0.01–0.001	0.01–0.001	<0.001			0.01–0.001		>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	0.05–0.001

The renal clearance of inulin was 100.3 ml. per minute, of para-aminohippurate, 322.2 ml. per minute, with a filtration fraction of 31.4 per cent. The renal fraction of the cardiac output was 13.1 per cent. The total plasma volume was 2.97 liters. The thoracic mean circulation time was 15.3 seconds.

The cases in group IV are divided in two subgroups: seven cases without right heart failure (table 3, *a* and *b*) and seven cases in right heart failure (table 4, *a* and *b*). In the group without right heart failure the mean heart volume was 796 ml. per square meter of body surface area, the pressure in the pulmonary artery was 52.6 mm. Hg, the pulmonary capillary venous pressure was 24.0 mm. Hg and the right auricular pressure, 1.6 mm. Hg. The cardiac index was 2.11 liters per minute per square meter of body surface area. The renal clearance of inulin was 76.3 ml. per minute, of para-aminohippurate, 216.4 ml. per minute, with a filtration fraction of 34.9 per cent. The renal fraction of the cardiac output was 10.8 per cent. The total plasma volume was 3.89 liters. The mean thoracic circulation time was 17.8 seconds.

In the seven patients in group IV with right heart failure, the mean heart volume was 873 ml. per square meter of surface area. The pressure in the pulmonary artery was 73.5 mm. Hg, the pulmonary capillary venous pressure was 24.8 mm. Hg and the right auricular pressure 10.4 mm. Hg. The mean cardiac index of the group was 1.82 ml. per minute per square meter of body surface area. The renal clearance of inulin was 72.0 ml. per minute, of para-aminohippurate, 158.4 ml. per minute, with a filtration fraction of 46.2 per cent. The renal fraction of the cardiac output was 9.12 per cent. The total plasma volume was 3.81 liters. The thoracic mean circulation time was 27.5 seconds.

Tables 5, 6 and 7 contain the observations made during exercise. In the cases in group I and II (table 5) exertion produced a significant increase in the pressures in the pulmonary circulation, in the arteriovenous oxygen difference and in cardiac output. The inulin clearances were not altered, but the para-aminohippurate clearance, the renal fraction of the cardiac output and the sodium excretion were decreased. The filtration fraction and the renal resistance increased during exercise. Findings recorded during exercise in the patients of groups III and IV, who were not in right heart failure (table 6), were in the same direction, differing only in numerical values from those in the former group. In the seven patients with right heart failure (table 7), on the contrary, the increase in arteriovenous oxygen difference during exertion was of such magnitude as to render the change in cardiac output insignificant. The pressures in the pulmonary artery and right auricle and the pulmonary capillary venous pressure rose. Exercise produced no change in inulin or para-aminohippurate clearance, nor in filtration fraction, renal

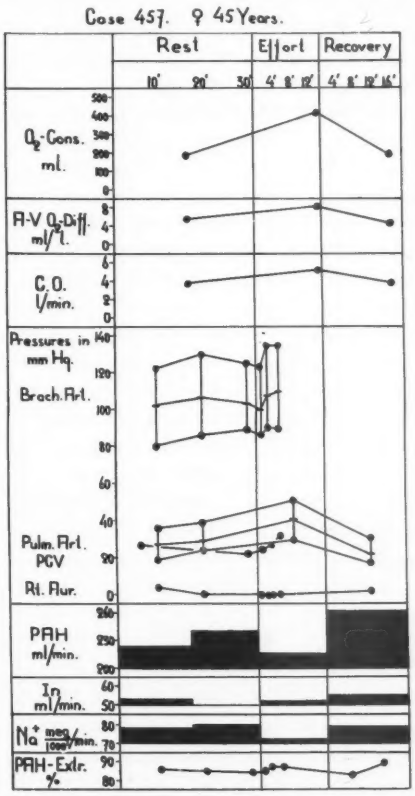


FIG. 1. Case 457. Female patient with mitral stenosis (group III). Hemodynamic and clearance values obtained on right heart and renal vein catheterization during rest and exercise. Effort did not cause any change in para-aminohippurate extraction.

TABLE 8.—*Seventy-two Cases of Mitral Stenosis Grouped According to Clearance of Para-aminohippurate as well as Clinical Criteria and Correlated with the Numerical Value of the Pulmonary Capillary Venous Pressure Divided by Cardiac Index (PCV/CI) and with Arteriovenous Oxygen Difference (A-V O_2 difference). Values for Groups Containing Three or Fewer Patients Are Given within Brackets*

	PCV/CI				A-V O_2 diff.			
	Gr I-II	III	IV	M	I-II	III	IV	M
PAH >350	3.43	6.99	—	4.8	36.9	46.8	—	40.7
PAH 350–220	4.63	9.10	(12.22)	8.1	46.1	53.7	(67.7)	52.6
PAH <220	—	(8.73)	(11.40)	10.26		(50.0)	(64.3)	58.2
Mean	3.86	8.40	11.75		40.5	51.2	65.7	

fraction of cardiac output or in renal resistance. The sodium excretion decreased significantly in this group also. Figure 1 demonstrates typical findings in one of the patients (case 459) in group III in whom a second catheter was left in the renal vein during the study. Exercise did not cause any change in para-aminohippurate extraction although the renal plasma flow decreased.

In table 8 the material has been grouped according to clinical criteria as well as para-aminohippurate clearance. These groups have subsequently been correlated according to arteriovenous oxygen difference and the numerical value of pulmonary capillary venous pressure divided by the cardiac index. The grouping according to changes in para-aminohippurate clearance gives the same distribution of arteriovenous oxygen difference and quotient for pulmonary capillary venous pressure divided by cardiac index as the clinical grouping. In the separate clinical groups, however, the cases with high para-aminohippurate clearance have a lower arteriovenous oxygen difference and quotient than the cases with low para-aminohippurate clearance, both being expressions of the severity of the disease.

DISCUSSION

Methods

When clearance determinations and heart catheterization are performed simultaneously, it is of primary importance to ascertain whether either investigation influences the results of the other. Several facts indicate that such influence is negligible. The most important reason for this assumption is the fact that in an earlier investigation in which heart catheterization and clearance studies were performed on separate days on the same subject the results obtained were almost identical with those obtained in the present study. The fact that identical clearance values were obtained in a group of normal subjects consisting of nurses and medical students when the heart was catheterized and when it was not is still another reason. Finally, disturbing factors have been methodically avoided during the investigation and no significant signs of anxiety or discomfort have been noticed during important measurements.[31, 35] Cardiac output and blood pressure values obtained during the present investigation are well in agreement with results obtained earlier.[14, 24, 34] It is concluded that the two investigations, heart catheterization and clearance studies, when performed simultaneously, do not significantly influence each other.

Another problem is, whether the administration of a single dose of inulin produces misleading clearance values for this substance. Fewer theoretic objections can be raised against the technic of administration by infusion than against administration of the material in a single dose. An unpublished study in which both methods were applied in normal subjects and in patients with different diseases showed that the average difference between results obtained with single dose and with drip administration is insignificant. The exception to this statement, the results in pregnant women and patients with hydronephrosis, are without bearing in this connection.

It has been shown earlier that a diet as nearly salt-free as possible and perhaps combined with mercurial diuretics results in a decrease in para-aminohippurate clearance. In the

present study a few patients received a salt-free diet, but this was never extreme (2 Gm. sodium chloride each day). Mercurial diuretics were also administered but in no case during the week preceding the investigation. The results obtained, therefore, cannot be attributed to any effect of desalting the patients.

In the present study the plasma volume was estimated by the injection of T-1824[28] through a heart catheter. The estimation of the dye remaining in the catheter increased the error of the method. The plasma volume was somewhat larger in the patients belonging to group IV and in the patients with right heart failure (irrespective of group) than in the remaining patients in groups I, II and III, who had normal plasma volume. This difference was, however, not significant (fig. 2).

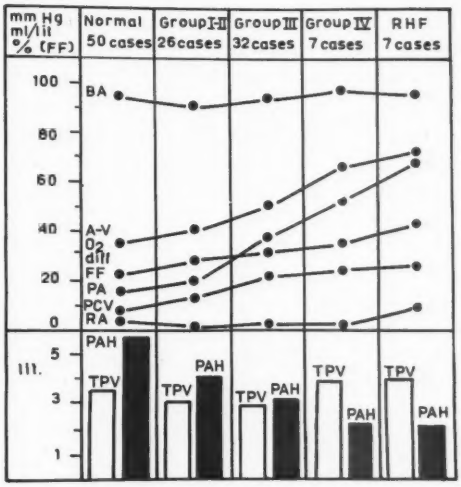


FIG. 2. Hemodynamic findings, values for total plasma volume, para-aminohippurate clearance, filtration fraction and oxygen difference in 50 normal individuals compared with the same values in 72 patients with mitral stenosis grouped according to functional capacity.

Results

Observations at Rest. It is probable that the surprisingly high and nearly always constant renal blood flow found in the majority of normal individuals is physiologic and necessary and is not an unnecessary strain on circulation and heart. In certain conditions which produce "supernormal" renal blood flow, such as pregnancy and fever, the need for this augmented flow can easily be understood. In normal subjects during conditions of stress, such as heavy work, renal blood flow can be lowered and in this way allow more blood to flow to other parts of the body. Thus the increase in cardiac output is kept within narrower limits. It is unknown whether this acute decrease of renal blood flow is of any importance for the kidneys. In patients with heart disease and lowered cardiac output a similar mechanism seems to operate even when the patient is resting.[34]

In our study renal blood flow was significantly lowered and there was good agreement between the pulmonary artery pressure and the degree of lowered blood flow, which confirms previous observations. Inulin clearance was moderately diminished. In groups I and II values obtained at rest were lower than normal, but not significantly so. In groups III and IV inulin clearance was significantly lowered but proportionately less so than the renal blood flow; that is, the filtration fraction was elevated. On the whole the sodium excretion during rest was lowered in proportion to the severity of the mitral stenosis, but, since the patients did not receive identical diets, this information is not very valuable.

As the severity of the mitral stenosis increased, the values for renal clearances obtained during rest more and more approached and even exceeded those obtained in normal individuals performing heavy work.

The opinion that the lowered renal blood flow in patients with heart disease is a change brought about by necessity would be less speculative if the lowering were functional and not the result of organic renal vascular change. That the lowered renal blood flow is functional seems probable since the low renal blood flow in patients with mitral stenosis can be raised to normal or nearly to normal values by the administration of Apresoline[35] or the infusion of large quantities of isotonic glucose solution (unpublished observations). This does not exclude the possible existence of organic damage, brought about, for instance, by emboli, but indicates only that such damage, if present, does not greatly diminish renal function. Fur-

ther evidence is provided by the fact that the para-aminohippurate extraction is normal in those patients with mitral stenosis in whom this has been investigated. The high filtration fraction is another factor which makes it highly improbable that the changes in clearance values should be due exclusively to embolic changes. Postmortem examinations have shown the existence of extremely low clearance values without the coexistence of any old emboli.

Other hemodynamic data in patients with mitral stenosis are already well-known and the present results corroborated earlier findings. During rest there was an increase in pulse rate, arteriovenous oxygen difference and pulmonary pressure, decrease in the cardiac index and arterial oxygen saturation, all these changes paralleling the severity of the disease.

Observations during Effort

Earlier investigations on the effect of exercise (in the recumbent position) in normal individuals have led to the following conclusions: (1) Light exercise raises the oxygen consumption up to the maximum of 500 ml. of oxygen per minute and does not significantly influence para-aminohippurate clearance, inulin clearance or sodium excretion. (2) Heavier exercise produces a marked lowering of para-aminohippurate clearance and sodium excretion. Inulin clearance seems to decrease but the material supporting this statement is too small to allow any definite conclusion. Inulin clearance, however, always decreases less than para-aminohippurate clearance; that is, the filtration fraction increases. The para-aminohippurate extraction is unaffected even by heavy exercise.[10]

When the effect of effort on renal function in patients with mitral stenosis is discussed, it is natural to divide the material into two groups: one containing patients with normal renal venous pressure and the other patients with pathologically elevated renal venous (or right auricular) pressure (that is, above 5 mm. Hg).

Response of Patients with Mitral Stenosis and with Normal Renal Venous Pressure. This group was not homogeneous but the values for renal clearances obtained in the resting individuals were proportional to the severity of the stenosis whether the valvular disease was classified by clinical criteria or by pulmonary arterial pressure (which is even better in patients with mitral stenosis).

The effect of light work on patients with mitral stenosis showed the same trend: as the severity of the heart disease increased, so did the filtration fraction while sodium excretion usually decreased. There appeared to be a minimum value for renal blood flow (roughly 150 to 200 ml. of plasma per minute). When the basal value was near this, effort did not, as a rule, produce any further marked decrease. The hemodynamic changes found already at rest were even more accentuated during exercise, paralleling the severity of the disease, with the exception of cardiac index which was low during rest but increased on effort though not nearly enough, the increase being smaller as the severity of the disease increased. Venous pressure varied within the normal range.

Response of Patients with Mitral Stenosis and Pathologically Increased Venous Pressure. In the patients of this group the average inulin clearance was relatively low at rest and decreased somewhat on effort. Clearance of para-aminohippurate, however, did not show any further decrease on exercise probably because renal blood flow had at rest already reached its lowest possible level mainly because of the low cardiac output, which did not allow any "superfluous" renal blood flow. As to hemodynamics, a low initial cardiac index, which increased slightly or not at all on exercise, was registered. Thus, the increased arteriovenous oxygen difference on exercise could almost be considered to be a direct measure of the increased oxygen consumption. The pulmonary artery pressure was somewhat higher in the patients of group IV with right heart failure than in those without failure, and increased further on effort. Neither index nor pulmonary artery pressure differences were significant, however, and arterial oxygen saturation remained virtually unchanged. Systemic venous pressure (or rather mean right auricular pressure) increased an average 4.7 mm. Hg on effort. Only one of the patients did not have an elevated right auricular pressure at rest. Thus, in the present study, the patients with normal

right auricular pressures at rest only experienced a slight rise on effort (recumbent) while the patients with elevated pressures showed a further, marked increase.

Apparently there was no difference in the para-aminohippurate clearance or the filtration fraction in patients with right heart failure and in patients without right heart failure, if consideration is given to the fact that patients with failure had a more deficient pulmonary circulation than patients without failure. (See figure 3).

Effort apparently did not markedly influence para-aminohippurate clearance in the group with venous pressure increase on exercise. This was due apparently to low perfusion during rest and not to the elevated venous pressure as such. (See figure 3*c*.) One conclusion can be drawn: the decrease in renal blood flow is not due to the elevation of venous pressure but to other effects of the insufficient circulation.[3, 4, 5]

Sodium Excretion

The changes in sodium excretion produced by heart disease are naturally of great interest when the pathogenesis of edema[6, 7, 26] is being discussed. Heart failure usually appears during or after effort. Consequently the effect of effort has been studied in the present material. As has been shown earlier, the correlation between changes in inulin clearance and changes in sodium excretion was poor. Of course it can be pointed out that inulin clearance is not necessarily a true measure of glomerular filtration, but this in no way solves the problem. Consequently other factors must be discussed.

As the reabsorption of sodium must by necessity be a process which demands energy, the oxygen consumption of the kidney naturally influences the excretion of sodium. Fishman and co-workers[17] have shown that a further lowering of an initially low arterial oxygen saturation in patients with "cor pulmonale" increases the excretion of sodium and that breathing oxygen (that is increasing the oxygen saturation) reduces the excretion. In the present material it can be said that when oxygen saturation was low so was sodium excretion, even though the correlation was not very good.

On effort, sodium excretion was reduced

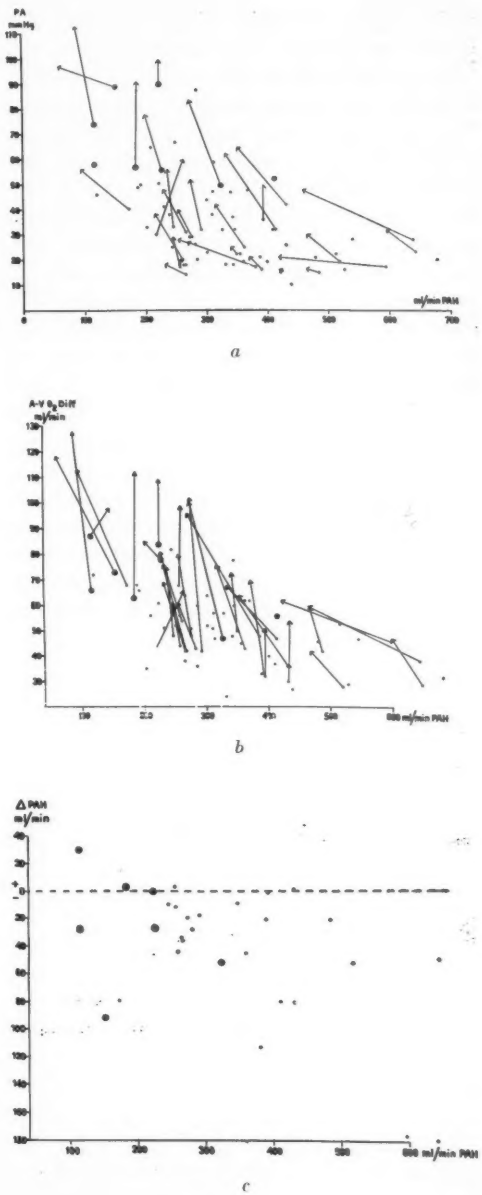
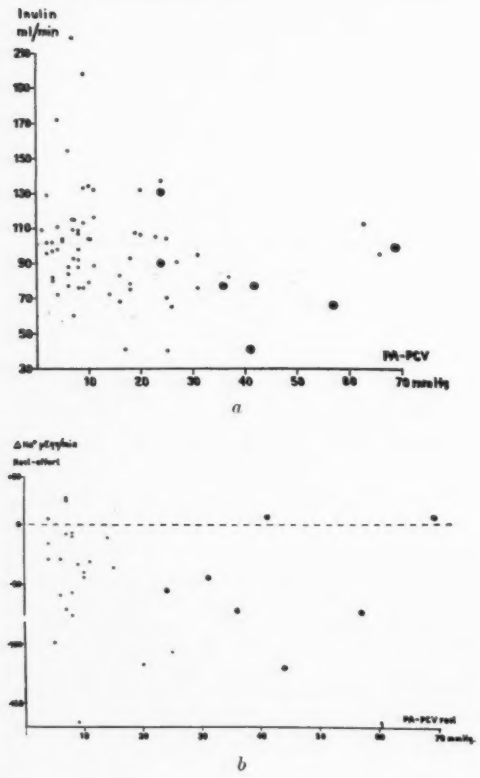


FIG. 3. Para-aminohippurate clearance in 72 patients with mitral stenosis correlated with (*a*) pulmonary arterial pressure and (*b*) oxygen difference. The arrows indicate the changes produced by exercise performed by 31 of these patients. In (*c*) the para-aminohippurate clearance has been correlated with changes in the same produced by exercise in said cases.

while oxygen saturation either remained unaltered or perhaps was somewhat reduced. Thus, in this study we did not find that sodium excretion was related to renal oxygen supply. The "cor pulmonale" study and the present study differ, however, in one very important respect: arterial oxygen saturation was low in the former, and (probably) venous oxygen saturation was low in our experiments. (See figure 5.) Consequently, it is probable that different parts of the renal capillary system were affected (by anoxia) in the two studies. This in turn would, at least theoretically, produce entirely different effects. The patients in this study in whom the oxygen saturation of renal venous blood has been measured are too few, however, to allow reliable comparison between this value and fluctuations in sodium excretion.

Breathing carbon dioxide has been said to reduce renal blood flow.[21] In our studies exercise resulted in a reduced renal blood flow and an elevated carbon dioxide tension. The relation of these findings to excretion of sodium must be discussed. It has been shown that breathing carbon dioxide (5 to 7 per cent), in recumbent position, does not influence sodium excretion at all but increases diuresis. This investigation also indicated that breathing carbon dioxide does not in any definite way influence renal blood flow if psychic irritation is avoided.[2]

Little is known of the influence of other metabolites on sodium excretion. However, in our patients not in right heart failure there was fair agreement between changes in sodium excretion and renal blood flow during exercise (fig. 6). It has been shown that in patients in whom exercise produces a rise in venous pressure the blood flow is practically unchanged while sodium excretion is reduced.[29] If the reduction in sodium excretion is to be explained hemodynamically, it seems necessary to postulate two different mechanisms. Changes in renal blood flow, however, cannot produce unmediated changes in sodium excretion. There



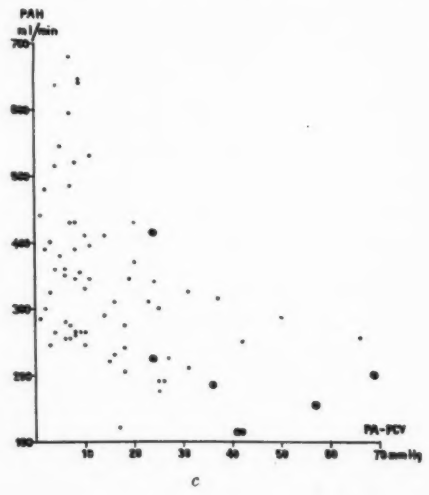


FIG. 4. Pulmonary resistance, that is, the difference between pulmonary arterial and pulmonary capillary venous pressure compared with (a) inulin clearance, (b) clearance of para-aminohippurate in 72 cases of mitral stenosis, 7 of which were in right heart failure (●) and with (c) changes in sodium excretion produced by effort in 31 cases of mitral stenosis. As can be seen no correlation exists between pulmonary resistance and these renal values.

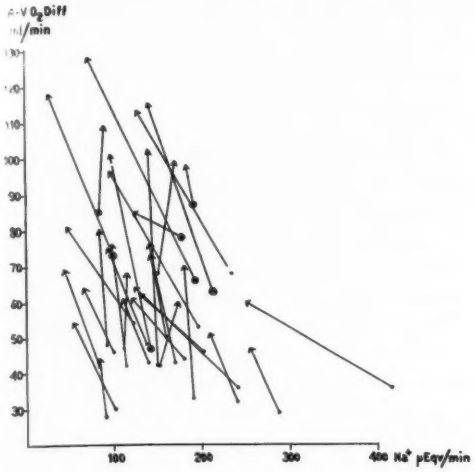


FIG. 5. Sodium excretion in 31 cases of mitral stenosis, 7 of these in right heart failure (○), correlated with oxygen difference. The arrows indicate the changes produced by exercise; on the whole, a fall in sodium excretion and a rise in oxygen difference.

must exist a factor which influences sodium excretion when renal venous pressure is elevated. With the technic used in the present investigation this possible hemodynamic factor cannot be exactly defined. Gomez' ingenious formula for estimation of resistance in different renal segments[18] cannot be applied since there must be great, though unmeasurable, variations in interstitial pressure, especially in our patients with right heart failure. It is open to doubt, however, whether a hemodynamic factor must be found in order to explain the changes in sodium excretion produced by exercise. It is equally possible that exercise releases hormones (noradrenaline? adrenaline?) which influence renal tubular function directly. A few of the patients of our series showed pathologically high noradrenaline excretion values, but these could not be correlated either with renal blood flow or sodium excretion. It will be necessary, therefore, to investigate more closely in what way hormones which decrease sodium excretion influence the kidney, especially hormones which are released quickly enough to produce an effect as rapidly as does exercise. The effect on the kidney of metabolites produced by exercise should also be investigated more closely.

In the present study, patients with right

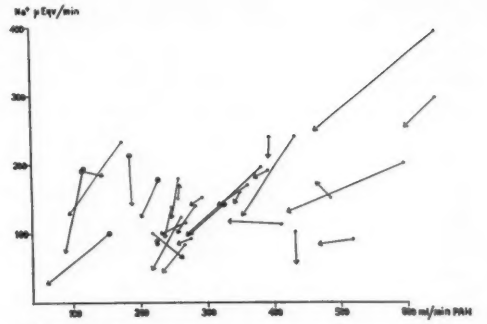


FIG. 6. Clearance of para-aminohippurate in 31 cases of mitral stenosis, 7 of these in right heart failure, correlated to sodium excretion. The arrows indicate the changes produced by effort.

heart failure differ from all the others only as to pulmonary vascular resistance (that is, the difference between pulmonary arterial and pulmonary capillary venous pressure). This resistance is much greater in patients with right heart failure, but it is not correlated with either inulin clearance during rest (fig. 4*a*) or changes in sodium excretion during effort (fig. 4*b*). Local conditions in the pulmonary circulation can therefore be considered as a more probable cause of the increased resistance than the incapability of the kidneys to excrete sodium and water.

SUMMARY

1. In 72 patients with mitral valvular disease, cardiac output, pulmonary arterial, pulmonary capillary venous and right auricular pressures were determined simultaneously with the renal clearance of inulin and para-aminohippurate, all patients being at rest and in the recumbent position.

In rough proportion to the severity of symptoms the cardiac output was reduced and the pressure in the pulmonary circulation increased. In only a few patients was the right auricular pressure elevated. The clearance of para-aminohippurate was decreased in all cases, likewise in rough proportion to the degree of alteration of the cardiodynamics. The inulin clearance showed much less alteration. There was no striking difference in those with and those without right heart failure.

2. In 31 patients the response to 15 to 17 minutes of steady, mild exercise in the recumbent position was studied.

In all patients not in right heart failure exercise produced a decrease in clearance of para-aminohippurate and sodium excretion and a increase in renal resistance. Similar exercise does not cause any change in renal clearances or sodium excretion in normal individuals. The cardiac output increased, as did the pressures in the pulmonary circulation. The right auricular pressure and the inulin clearance were unaltered.

In the patients in right heart failure exercise produced no increase in cardiac output, but it did produce an increase in the pressures in the pulmonary circulation. While exercise resulted in only slight change in clearance of para-aminohippurate and inulin, in the filtration fraction and in renal resistance it did result in increase in the renal venous pressure and the sodium excretion decreased.

3. These findings are briefly discussed.

Sumario Español

1. En 72 pacientes con enfermedad valvular mitral las presiones, arterial pulmonar, capilar pulmonar, auricular derecha y producción cardíaca fueron determinadas simultaneamente con la depuración renal de inulina y paraminohipurato, todos los pacientes estando en descanso y en la posición reclinada.

En proporción tosca a la severidad de los síntomas la producción cardíaca fué reducida y la presión en la circulación pulmonar aumentada. En solo muy pocos pacientes la presión auricular derecha estuvo elevada. La depuración de paraminohipurato estuvo disminuida en todos los casos, de igual manera en tosca proporción al grado de alteración de la cardiodinámica. La depuración de inulina mostró mucho menor alteración. No hubo diferencias significativas en aquellos con o sin decompensación cardíaca del lado derecho.

2. En 31 pacientes la repuesta a 15 o 17 minutos de ejercicio moderado continuo en la posición reclinada fué estudiada.

En todos los pacientes que no tenian decompensación del lado derecho del corazón el ejercicio produjo un decremento en la depuración de paraminohipurato y excreción de sodio y un incremento en resistencia renal. Ejercicio similar no causa nigún cambio en depuración renal o excreción de sodio en el individuo normal. La producción cardíaca total aumentó, como así las presiones en la circulación pulmonar. La presión auricular derecha y la depuración de inulina permanecieron inalteradas.

En los pacientes con decompensación cardíaca del lado derecho el ejercicio no produjo un aumento en producción total cardíaca pero produjo un aumento en las presiones de la circulación pulmonar. Aunque el ejercicio resultó en un ligero cambio en la depuración de paraminohipurato e inulina, en la fracción de filtración y en la resistencia renal, esto, resultó en un aumento en presion venosa renal y la excreción de sodio disminuyó.

3. Estos hallazgos son brevemente discutidos.

REFERENCES

[1] Aas, K., and Blegen, E.: The renal blood flow and the glomerular filtration rate in congestive heart failure and some other clinical conditions. Scandinav. J. Clin. & Lab. Investigation **1**: 22, 1949.

[2] Barbour, A., Bull, G. M., Evans, B. M., Jones, N. C. H., and Logothetopoulos, J.: The effect of breathing 5 to 7 per cent carbon dioxide on urine flow and mineral excretion. Clin. Sc. **12:** 1, 1953.

[3] Berne, R. H., and Levy, M. N.: Effects of acute reduction of cardiac output on the renal circulation of the dog. J. Clin. Investigation **29:** 444, 1950.

[4] Blake, W. D., Wégria, R., Keating, R. P., and Ward, H. P.: Effect of increased renal venous pressure on renal function. Am. J. Physiol. **175:** 1, 1949.

[5] Bradley, S. E., and Bradley, G. P.: The effect of increased intra abdominal pressure on renal function in man. J. Clin. Investigation **26:** 1010, 1947.

[6] Briggs, A. P., Fowell, D. M., Hamilton, W. F., Remington, J. W., Wheeler, N. C., and Winslow, J. A.: Renal and circulatory factors in the edema formation of congestive heart failure. J. Clin. Investigation **27:** 810, 1948.

[7] Brod, J., and Fejfar, Z.: The origin of oedema in heart failure. Quart. J. Med., New Series **19:** 187, 1950.

[8] Bucht, H.: Examination of the renal plasma flow by means of para-aminohippuric acid (PAH) using one intramuscular injection. Scandinav. J. Clin. & Lab. Investigation **1:** 126, 1949.

[9] —— Studies on renal function in man. Scandinav. J. Clin. & Lab. Investigation **3** (Suppl. 3): 1, 1951.

[10] ——, Ek, J., Eliasch, H., Holmgren, A., Josephson, B., and Werkö, L.: The effect of exercise in the recumbent position on the renal circulation and sodium excretion in normal in-

dividuals. Acta physiol. scandinav. **28:** 95, 1953.

[11] COURNAND, A., AND RANGES, H. A.: Catheterization of the right auricle in man. Proc. Soc. Exper. Biol. & Med. **46:** 462, 1941.

[12] Nomenclature and criteria for diagnosis of diseases of the heart and blood vessels, ed. 5. The Criteria Committee of the New York Heart Association Inc. New York, 1953.

[13] EICHNA, L. W., FARBER, S. J., BERGER, A. R., EARLE, D. P., RADER, B., PELLEGRINO, E., ALBERT, R. E., ALEXANDER, D. J., TAUBE, H., AND YOUNGWIRTH, S.: Cardiovascular dynamics, blood volumes, renal functions and electrolyte excretions in the same patients during congestive heart failure and after recovery of cardiac compensation. Circulation **7:** 674, 1953.

[14] ELIASCH, H.: The pulmonary circulation at rest and on effort in mitral stenosis. Scand. J. Clin. & Lab. Investigation **4** (suppl. 4): 1, 1952.

[15] —, WADE, G., AND WERKÖ, L.: The effects of work on the pulmonary circulation in mitral stenosis. Circulation **5:** 271, 1952.

[16] —, VARNAUSKAS, E., AND WERKÖ, L.: Exercise tests in heart diseases. Nord. med. **49:** 776, 1953.

[17] FISHMAN, A. P., MAXWELL, M. A., GROWDER, C. H., AND MORALES, P.: Kidney function in cor pulmonale. Particular consideration of changes in renal hemodynamics and sodium excretion during variations in level of oxygenation. Circulation **3:** 703, 1951.

[18] GOMEZ, D. M.: Calculation of effective afferent and efferent renal resistance. Federation Proc. **7:** 41, 1948.

[19] GROSSMAN, J., WESTON, R. E., HALPERIN, J. P., AND LEITER, L.: The nature of the renal circulatory changes in chronic congestive failure as reflected by renal tubular maximal functions. J. Clin. Investigation **29:** 1320, 1950.

[20] HELLER, B. I., AND JACOBSON, E. W.: Renal hemodynamics in heart disease. Am. Heart J. **39:** 188, 1950.

[21] HOOD, B.: Studies on the renal function. The effect of inhalation of carbon dioxide on renal clearances in normals. Thesis. Published by the author. Falun, Sweden, 1950.

[22] LAGERLÖF, H. AND WERKÖ, L.: Studies on the circulation in man. I. Technique of venous catheterization with determination of cardiac output and simultaneous recordings of the blood pressures, the electrocardiogram, phonocardiogram and respiration. Acta med. scandinav. **132:** 495, 1947.

[23] —, AND —: Studies on the circulation in man. VI. The pulmonary capillary venous pressure pulse. Scandinav. J. Clin. & Lab. Investigation **1:** 147, 1949.

[24] —, —, BUCHT, H., AND HOLMGREN, A.: Lungenzirkulation bei Herzinsuffizienz. Verhandl. deutsch. Gesellschaft Kreislaufforsch. **15:** 213, 1949.

[25] MAXWELL, M. H., BREED, E. S., AND SCHWARTZ, I. L.: Renal venous pressure in chronic congestive heart failure. J. Clin. Investigation **29:** 342, 1950.

[26] MERRILL, A. J.: Edema and decreased renal blood flow in patients with chronic congestive heart failure: evidence of "forward failure" as the primary cause of edema. J. Clin. Investigation **25:** 389, 1946.

[27] —, AND CARGILL, W. H.: The effect of exercise on the renal plasma flow and filtration rate of normal and cardiac subjects. J. Clin. Investigation **27:** 272, 1948.

[28] NOBLE, R. P., AND GREGERSEN, M. I.: Blood volume in clinical shock. I. Mixing time and disappearance-rate of T-1824 in normal subjects and in patients in shock; determination of plasma-volume in man from 10-minute sample. J. Clin. Investigation **25:** 158, 1946a.

[29] SELKURT, E. E., HALL, P. W., AND SPENCER, M. P.: Response of renal blood flow and clearance to graded partial obstruction of the renal vein. Am. J. Physiol. **157:** 40, 1949.

[30] SINCLAIR-SMITH, B., KATTUS, A. A., GENEST, J., AND NEWMAN, E. V.: Changes in the renal mechanisms of electrolyte excretion and the metabolic balances of electrolytes and nitrogen in congestive cardiac failure with exercise, rest and aminophyllin. Bull. Johns Hopkins Hosp. **84:** 369, 1949.

[31] STEVENSON, I. P., DUNCAN, C. H., AND WOLFF, H. G.: Circulatory dynamics before and after exercise in subjects with and without structural heart disease during anxiety and relaxation. J. Clin. Investigation **28:** 1534, 1949.

[32] TYBJAERG-HANSEN, A.: Pressure-measurement in the human organism. Copenhagen, Teknisk Forlag, 1949.

[33] WARREN, J. V., MERRILL, A. J., AND BRANNON, E. S.: Observations on renal venous blood in normal unanesthetized subjects and patients with severe congestive heart-failure. J. Clin. Investigation **23:** 928, 1944.

[34] WERKÖ, L., EK, J., BUCHT, H. AND ELIASCH, H.: Correlation between renal dynamics, cardiac output and right heart pressures in mitral valvular disease. Scandinav. J. Clin. & Lab. Investigation **4:** 15, 1952.

[35] —, VARNAUSKAS, E., EK, J., BUCHT, H., THOMASSON, B., BERGSTRÖM, J., AND ELIASCH, H.: Studies on the renal circulation and renal function in mitral valvular disease. II. Effect of Apresoline. Circulation **9:** 700, 1954.

[36] WOLF, S., AND WOLFF, H. G.: A summary of experimental evidence relating life stress to the pathogenesis of essential hypertension in man Hypertension. A symposium edited by E. T. Bell. Minneapolis, University of Minnesota Press, 1951. P. 288.

Studies on the Renal Circulation and Renal Function in Mitral Valvular Disease

II. Effect of Apresoline

By Lars Werkö, M.D., Edvardas Varnauskas, M.D., Jan Ek, M.D., Härje Bucht, M.D., Bengt Thomasson, M.D., Jonas Bergström, M.K., and Harald Eliasch, M.D.

In a study of the nature of the renal changes in patients with mitral stenosis, lowered renal function and reduced renal circulation the effect of Apresoline, given during heart catheterization to 12 patients with mitral stenosis of varying severity, was studied. The drug was found to increase renal blood flow (and decrease arterial blood pressure), showing that the renal changes in mitral stenosis are reversible. The two effects of Apresoline were shown to be independent of each other.

IN PATIENTS with mitral stenosis, with or without right heart failure, renal blood flow is greatly reduced. We have shown previously the existence of a certain correlation between the severity of the stenosis and degree of reduction of renal blood flow. Whether this change in renal blood flow is the result of organic vascular changes (for example, emboli) or represents a functional manifestation of the kidney's role as a regulator of the circulatory system is as yet unknown. Fever and pregnancy have so far been the only known stimuli producing increased renal blood flow in patients with hypertension and reduced renal blood flow. Neither of these procedures, however, can be used in studying the decrease of renal blood flow in patients with mitral stenosis. Reubi[12] has shown how Apresoline increases renal blood flow in patients with hypertension. We have studied the effect of this drug on patients with mitral stenosis in order to establish the character of the coexisting renal change.

Methods and Materials

In 11 cases of mitral stenosis of varying severity and duration, the effect of Apresoline has been studied in acute experiments during which para-aminohippurate, inulin, creatinine clearance and sodium excretion were measured simultaneously with the determination of cardiac output and registration of the pulmonary and systemic pressures. Cardiac catheterization was performed according to the method of Cournand and Ranges and the pressures were measured with Tybjaerg-Hansens electrical manometer. Cardiac output was determined by application of the Fick principle. Para-aminohippurate and inulin were administered by intravenous drip and urine was collected every 15 minutes. After two basal periods, Apresoline and noradrenaline were added to the drip, which delivered 0.3 to 0.5 mg. of Apresoline per minute and 0.006 mg. of noradrenaline per minute, respectively. As a rule, Apresoline administration was discontinued after 30 minutes when 10 to 15 mg. had been given. Subsequently only noradrenaline was given during the following 15 to 30 minutes. Pressures were registered almost continuously and cardiac output was determined several times during these periods. Four of the patients performed light work, equaling approximately 70 kilogrammeters per minute (cycle ergometer) lying on their backs, immediately following Apresoline administration. In cases with mitral stenosis this effort ordinarily reduces renal blood flow by 15 per cent.

From the IVth Medical Service and Central Laboratory, St. Erik's Hospital, Stockholm, Sweden.

Aided by grants from the Swedish Medical Research Council and the Wallenberg Foundation.

Results

Table 1 lists para-aminohippurate clearance, filtration fraction, cardiac output and blood pressure before and during maximal Apresoline effect. Despite the fact that noradrenaline was given to maintain arterial blood pressure, a slight decrease was recorded while para-aminohippurate clearance and cardiac output increased. Figure 1 shows that as Apresoline-noradrenaline was given there was an immediate decrease of renal blood flow and increase of blood pressure, due to noradrenaline. After 15 minutes renal blood flow increased,

TABLE 1.—*The Effect of Apresoline on Para-aminohippurate Clearance, Filtration Fraction, Cardiac Output, Systemic and Pulmonary Pressures in 11 Patients with Mitral Stenosis*

Case no.	PAH		FF		C.O.		Brach.		P.A.		PCV	
	Basal	Apre-soline	Basal	Apre-soline	Basal	Apresoline	Basal	Apre-soline	Basal	Apre-soline	Basal	Apre-soline
498	413	571	32	25	4, 7	9, 3	88	78	53	65	29	28
526	239	458	31	23	2, 9	4, 4	84	76	38	44	20	—
529	192	1125	21	7, 3	2, 8	5, 1	115	88	50	56	25	—
536	344	377	31	35	3, 3	4, 8	106	105	37	37	18	—
554	301	355	34	34	5, 7	6, 0	69	61	23	32	21	21
500	625	690	25	26	8, 7	12, 2	95	95	12	12	5	4
534	569	720	21	17	11, 7	10, 9	98	93	10	10	7	4
569	121	166	34	30	3, 4	4, 9	80	61	46	63	29	—
571	419	621	23	19	6, 6	6, 2	96	77	22	23	19	—
598	300	285	27	19	7, 1	8, 1	86	79	18	20	8	10
604	340	424	38	32	5, 7	5, 8	105	88	41	45	25	22
Mean.....	351	527	29	24	5, 7	7, 1	93	82	32	37	19	—

and blood pressure fell as the Apresoline effect gradually predominated.

Table 2 shows the results obtained when work was performed during the Apresoline effect. Cardiac output increased, renal blood flow either remained unchanged or increased. Figure 2 shows an illustrative case. In figure 3 the effect produced by effort, as mentioned above, in 14 patients with mitral stenosis is

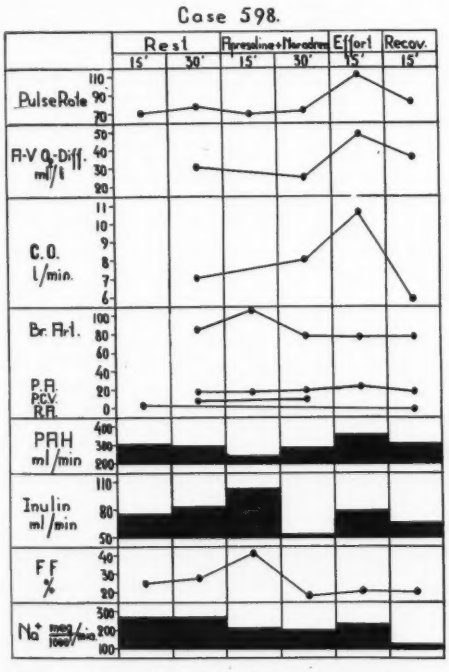


FIG. 1. (Case 598.) A female patient aged 38 who had rheumatic fever at the age of 28. Diagnosis: mitral stenosis, class II.[10]

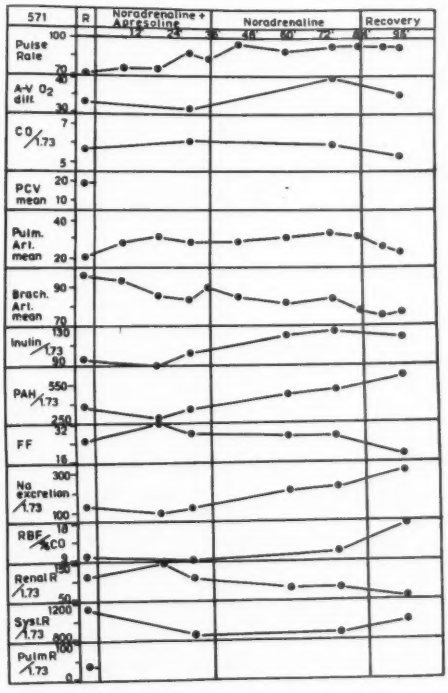


FIG. 2. (Case 571.) A female patient aged 43, who gave no history of rheumatic fever. Diagnosis: mitral stenosis, class II. (See fig. 1.)

TABLE 2.—*The Combined Effect of Apresoline and Exercise on Para-aminohippurate Clearance, Filtration Fraction, Cardiac Output, Systemic and Pulmonary Pressures in Four Patients with Mitral Stenosis*

Case	Rest		Apresoline		Exercise	Rest	
	I	II	I	II			
500	665	608	690	588	663	557	PAH
BSA	169	152	176	143	156	152	Inulin
1, 82	25	25	26	24	24	27	FF
	298	322	287	236	72	91	Na
	113	113	111	109	133	113	Pulse rate
	—	31	—	24	62	33	A-V diff.
	—	8, 7	—	12, 2	11, 4	7, 9	CO/1, 73
	—	95	96	95	105	63	Br. A
	—	12	14	—	18	—	PA
	—	4	4	9	7	—	PCV
		−2	−4	−1	+1	—	RA
534	629	527	502	710	680	604	PAH
BSA	124	114	112	115	121	106	Inulin
1, 70	20	22	22	16	18	18	FF
	357	287	304	359	335	302	Na
	86	107	111	122	142	125	Pulse rate
		26		24	36	32	A-V diff.
		11, 7		10, 9	15, 2	7, 9	CO/1, 73
		98	90	93	88	82	Br. A
		10	10	—	10	—	PA
	7	—	—	5	4	—	PCV
	1	—	—	—	0	0	RA
604	396	292	—	424	474	629	PAH
BSA	148	113		137	128	139	Inulin
1, 44	37	39	—	32	27	22	FF
	314	280	—	308	252	288	Na
	93	93	—	77	102	—	Pulse rate
		47	—	48	64	—	A-V
		5, 7	—	5, 8	7, 4	—	CO/1, 73
		105	—	88	78	—	Br. A
		41	—	45	45	—	PA
		25	—	22	25	—	PCV
		—	—	—	2	—	RA
598	305	297	242	285	358	311	PAH
BSA	76	83	102	53	79	66	Inulin
1, 79	25	28	42	19	22	21	FF
	270	271	209	201	235	124	Na
	71	78	70	75	113	84	Pulse rate
	—	31	—	26	49	37	A-V
	—	7, 1	—	8, 1	10, 7	6, 0	CO/1, 73
	—	86	108	79	78	78	Br. A
	—	18	18	20	25	18	PA
	—	8	—	10	—	—	PCV
	4	—	—	—	—	0	RA

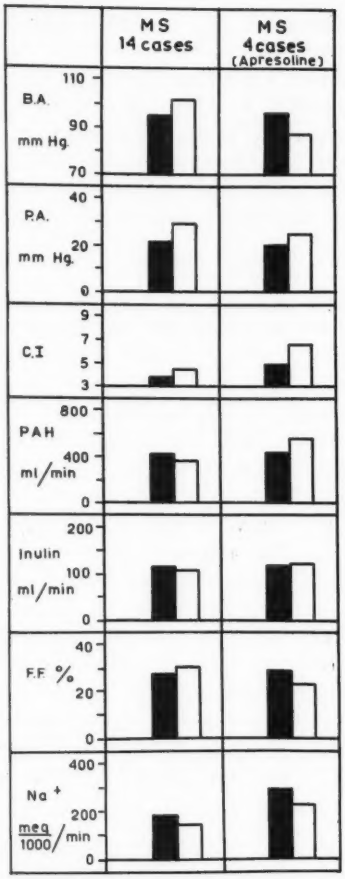


FIG. 3. Left: Mean values at rest in 14 patients with mitral stenosis (black columns) and on effort (white columns). Right: Corresponding values in four patients with mitral stenosis who were given Apresoline. Para-aminohippurate clearance is increased and brachial artery pressure is lowered; that is, the regular effect of exercise is supressed.

compared with the effect of equal effort in four comparable patients who were given 10 to 15 mg. of Apresoline.

DISCUSSION

At an early stage of this work we found that even a small amount of Apresoline may produce a marked fall in blood pressure and a shock-like state. It was found necessary, therefore, not only to give the drug in a small dose, but also to administer simultaneously a blood pressure raising agent. Noradrenaline satisfactorily met this requirement. This drug increases blood pressure and reduces renal blood flow. Moreover, while it allows satisfactory control of blood pressure, it does not interfere markedly with the effect of Apresoline on the kidneys. As this effect is obtained 15 to 20 minutes after administration, a single intravenous dose was found to be impractical and an intravenous drip at the rate of 0.5 mg. Apresoline per minute was used. In the same drip 0.006 mg. noradrenaline per minute was also given. This procedure resulted in a slight fall in arterial blood pressure with a simultaneous increase of renal blood flow, in certain cases amounting to several hundred per cent of the original flow. Consequently, these experiments show that in most cases of mitral stenosis the low renal blood flow is due to reversible, functional changes. This is of great importance when deciding whether a patient should be operated upon or not. If the patient is found to have seriously damaged kidneys, an operation is, of course, of very little avail.

Furthermore, Apresoline counteracts the effect which physical effort exerts on renal function in patients with mitral stenosis. Without Apresoline even slight work usually reduces renal blood flow as well as sodium excretion. When Apresoline is given, subsequent effort does not reduce renal blood flow; in some cases blood flow is even augmented. This may be due (1) to an inability of the renal vessels to react to adrenaline-noradrenaline or (2) to the fact that Apresoline inhibits the production of nervous impulses or hormones usually induced by effort. The effect of combined Apresoline-noradrenaline supports the former of these two theories.

The present investigation shows that noradrenaline suppresses the effect of Apresoline on arterial pressure while the effect on renal blood flow is unaffected. This indicates that the twofold effect of Apresoline is mediated by two independent mechanisms. Similar results have been obtained in hypertensive patients. It is improbable that the lowering of arterial pressure is secondary to the renal effect.

As has been shown earlier by Wilkinson and

co-workers, Apresoline does not influence the contraction or dilatation of the pulmonary vessels.

In our study we found an increase in pulmonary pressures parallel to increase in cardiac output. This may have been due to a combined effect of noradrenaline and Apresoline. Wilkinson and co-workers found that renal blood flow generally increased proportionally less than stroke volume did and concluded that Apresoline constitutes a selective vasodilator. Only when stroke volume and renal blood flow are measured simultaneously can there be any correlation made among the values obtained. Moreover, para-aminohippurate clearance is not an exact measure of changes in renal blood flow as the renal extraction of para-aminohippurate apparently is influenced by Apresoline. Renal vein catheterization performed in two patients with hypertension, showed that para-aminohippurate extraction fell from 90 to 80 per cent with a corresponding increase of renal plasma flow from 110 to 120 per cent of para-aminohippurate clearance. In our study on patients with mitral stenosis renal plasma flow was highly dependent on the arterial pressure.

Sodium excretion showed rather large variations in our study. If arterial blood pressure was maintained at a steady or almost steady level, sodium excretion paralleled the para-aminohippurate clearance. When a marked fall in arterial blood pressure was produced, decreasing inulin clearance, the values of sodium excretion reached very low levels. Apresoline influences sodium excretion only when a marked fall in blood pressure is produced. This may be due either to reduced filtration or to changes in arterial pressure.

Summary

1. To 11 patients with mitral stenosis 10 to 15 mg. of Apresoline was administered by intravenous drip at the rate of 0.3 to 0.5 mg. per minute. Noradrenaline was given simultaneously at the rate of 0.006 mg. per minute to counteract the hypotonic effect of Apresoline.

2. Renal blood flow increased, in some cases by several hundred per cent, showing that the renal changes in mitral stenosis are functional and reversible.

3. When Apresoline was given, renal blood flow was not, as otherwise, reduced on effort. Cardiac output, however, increased.

4. The two effects of Apresoline, increase of renal blood flow and lowering of arterial blood pressure are not interdependent.

Sumario Español

1. A 12 pacientes con estenosis mitral se les administró Apresolina intravenosa en cantidades de 10 a 15 mg. a una velocidad promedio de 0.3 a 0.5 mg. por minuto. Simultaneamente se administró Noradrenalina a una velocidad promedio de 0.006 mg. por minuto para contrarrestar el efecto hipotónico de la Apresolina.

2. La circulación renal aumentó, en algunos casos por varios cientos por ciento, demostrando que los cambios renales en la estenosis mitral son funcionales y reversibles.

3. Cuando la Apresolina se administró, la circulación renal no se redujo como se esperaría con el esfuerzo. La producción total cardíaca, sinembargo, aumentó.

4. Los dos efectos de la Apresolina, aumento en circulación renal y diminución de la presión arterial no son dependientes el uno del otro.

REFERENCES

[1] Bradley, S. E., Chasis, H., Goldring, W., and Smith, H. W.: Hemodynamic alterations in normotensive and hypertensive subjects during the pyrogenic reaction. J. Clin. Invest. **24:** 749, 1945.

[2] Bucht, H.: Examination of the renal plasma flow by means of para-aminohippuric acid (PAH) using one intramuscular injection. Scandinav. J. Clin. & Lab. Invest. **1:** 126, 1949.

[3] —: Studies on renal function in man. Scandinav. J. Clin. & Lab. Invest. **3:** suppl. 3, 1951.

[4] Chasis, H., Ranges, H. A., Goldring, W., and Smith, H. W.: The control of renal blood flow and glomerular filtration in normal man. J. Clin. Invest. **17:** 683, 1938.

[5] Eliasch, H.: The pulmonary circulation at rest and on effort in mitral stenosis. Scandinav. J. Clin. & Lab. Invest. **4:** suppl. 4, 1952.

[6] —, Wade, G., and Werkö, L.: The effects of work on the pulmonary circulation in mitral stenosis. Circulation **5:** 271, 1952.

[7] Freis, E. D., MacKay, J. C., and Oliver, W. F.: The effect of "sympatholytic" drugs on th-

cardiovascular response of epinephrine in man. Circulation **3:** 254, 1951.

[8] LAGERLÖF, H., AND WERKÖ, L.: Studies on the circulation in man. I. Technique of venous catheterization with determination of cardiac output and simultaneous recordings of the blood pressures, the electrocardiogram, phonocardiogram and respiration. Acta med. scandinav. **132:** 495, 1947.

[9] —, AND —: Studies on the circulation in man. VI. The pulmonary capillary venous pressure pulse. Scandinav. J. Clin. & Lab. Investigation **1:** 147, 1949.

[10] Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Blood Vessels, ed. 5. The Criteria Committee of the New York Heart Association Inc. New York, 1953.

[11] REUBI, F. C.: Influence de quelques vasodilateurs périphériques sur le flux sanguin rénal. Helvet. med. acta **16:** 297, 1949.

[12] —: Renal hyperemia induced in man by a new phthalazine derivative. Proc. Soc. Exper. Biol. & Med. **73:** 102, 1950.

[13] SELKURT, E. E., HALL, P. W., AND SPENCER, M. P.: Response of renal blood flow and clearance to graded partial obstruction of the renal vein. Am. J. Physiol. **147:** 40, 1949.

[14] TYBJAERG-HANSEN, A.: Pressure-measurement in the human organism. Copenhagen, Teknisk Forlag, 1949.

[15] WERKÖ, L., EK, J., ELIASCH, H., VARNAUSKAS, E., HOLMGREN, A., AND BUCHT, H.: The effect of Apresoline on pulmonary and renal hemodynamics in hypertensive cardiovascular disease and mitral stenosis. Nord. med. **49:** 397, 1953.

[16] —, BUCHT, H., JOSEPHSON, B., AND EK, J.: The effect of noradrenaline and adrenalin on renal hemodynamics and renal function in man. Scandinav. J. Clin. & Lab. Invest. **3:** 255, 1951.

[17] —, VARNAUSKAS, E., EK, J., BUCHT, H., THOMASSON, B., BERGSTRÖM, J., AND ELIASCH, H.: Studies on the renal circulation and renal function in mitral valvular disease. I. Effect of exercise. Circulation **9:** 687, 1954.

[18] WILKINSON, E. L., BACKMAN, H., AND HECHT, H. H.: Cardiovascular and renal adjustments to a hypotensive agent (1-hydrazinophthalazine: Ciba BA-5968: Apresoline). J. Clin. Invest. **31:** 872, 1952.

Ventricular Function

I. Starling's Law of the Heart Studied by Means of Simultaneous Right and Left Ventricular Function Curves in the Dog

By STANLEY J. SARNOFF, M.D., AND ERIK BERGLUND, M.D.

Starling's law of the heart has been studied in the dog with a complete circulation with the continuous registration of cardiac output, and atrial and arterial pressures. From this data ventricular function curves were constructed. In any given physiologic state there was a consistent and reproducible correlation between atrial pressure and ventricular stroke work on the same side. The classically conceived descending limb did not occur in the normal heart. The concept of a family of Starling or ventricular function curves adds a third dimension to the adaptive capacity of the heart as put forth by Frank and Starling.

STARLING'S LAW of the heart states "that the energy of contraction, however measured, is a function of the length of the muscle fibers" prior to contraction.[1] Starling deduced this law from his own and also from the prior studies of Frank on isolated heart and heart-lung preparations.[2-4] Both its validity and significance in the presence of an intact circulation have been questioned.[5-11] Many investigations of this matter in the presence of a complete circulation have been either inadequate or misleading largely because of the following: (1) stroke volume or cardiac output and not *stroke work* has been used as the measure of the "energy of contraction"; (2) attempts have been made to correlate right sided filling pressure with left ventricular stroke work; (3) attempts have been made to correlate filling pressure with ventricular work per minute instead of per stroke, and (4) perhaps most important, it has not been generally appreciated that a single Starling curve cannot always satisfactorily explain the observed phenomena; for any given heart there is a series or family of curves.

From the Department of Physiology, Harvard School of Public Health, Boston, Mass.

Supported by a grant in aid from the National Heart Institute, United States Public Health Service and a Basic Science Grant from Sharp & Dohme, Inc., Philadelphia, Pa.

Presented before the New Haven Heart Association, Feb. 5, 1953, and the National Heart Hospital, London, England, Feb. 12, 1953.

Further, the views of Starling and subsequent workers[1, 8, 12, 13, 41] led to the firmly entrenched concept that there is a significant descending limb of the curve at high filling pressures. Data will be presented below which support the interpretation that a descending limb occurs when the function of the myocardium is compromised but not in the normal heart.

An investigation has been started in this laboratory to evaluate more completely the law of the heart and the physical determinants of ventricular work in the living animal with a complete circulation. The objectives of this communication will be (1) to describe a method by means of which myocardial contractility can be quantitated in the dog with a complete circulation and the effect of any given physiologic or pharmacologic intervention can be more precisely appreciated; (2) to present data concerning the relationship between filling pressure and ventricular stroke work under a variety of physiologic circumstances and to examine these data in relation to the validity of Starling's law of the heart; and (3) to present data in support of a unifying concept, the family of Starling or ventricular function curves, which may help to reconcile previously conflicting views.

The data will be presented as right and left *ventricular function curves*. These curves are obtained by plotting the ventricular work in grammeters per stroke against the mean atrial

pressure on the same side. That aspect of Starling's law which deals with myocardial oxygen consumption will not be dealt with in this communication.

Method

Mongrel dogs weighing 12 to 28 Kg. but generally over 16 Kg. were anesthetized with morphine sulfate, 4 mg. per kilogram and 20 minutes later chloralose, 48 mg. per kilogram, and urethane, 480 mg. per kilogram. After starting positive pressure breathing, the chest was opened with the dog in the right oblique position and the left ribs 3, 4 and 5 and sometimes 2 were removed. Systemic blood flow (cardiac output minus coronary flow) was continuously recorded with a Potter Electroturbinometer.* The performance characteristics of this flowmeter and its application to the measurement of systemic blood flow have been described.[14, 15] In some experiments left main coronary artery flow was also recorded with the rotameter of Shipley and Wilson.[16-18] Full pulse pressures and electrically integrated mean pressures were measured with Sanborn Electromanometers.[19] These were obtained from a catheter in the right atrium through the left femoral vein, one in a lobular branch of the left pulmonary artery, one in the left atrium through a lobular pulmonary vein, and one in the aortic arch. All data were continuously recorded on a four channel direct-writing oscillograph. An electronic switching device (Sanborn Triplexer) made it possible to record five or six simultaneous events on four channels. The midlevel of the tricuspid valve was used as the zero reference for right atrium and pulmonary artery pressures. The midlevel of the mitral valve was used as the baseline for left atrial and aortic pressures.

A cannula was inserted into either the right or left atrium through a small opening in the pericardium. This communicated with a heated reservoir by means of Tygon tubing. The reservoir contained 6 per cent Dextran† in 0.9 per cent sodium chloride which was thoroughly mixed with the dog's blood prior to obtaining the ventricular function curves. Lowering of the hematocrit by Dextran does not alter the ventricular function curve until anemia becomes marked.[20] In the more recent experiments, blood from a donor dog was used in the reservoir instead of Dextran. This was then thoroughly mixed with the blood of the experimental dog.

By changing the height of the reservoir, the pressures in both atria could be varied over wide ranges just as by infusing or bleeding the dog through a femoral vein; the latter route has been used in more recent experiments. The pericardium either remained intact except for the small opening through which the reservoir tubing passed or was widely opened.

The blood was rendered incoagulable with Treburon.* An attempt was made to maintain body temperature by means of a heating pad under the dog. High bilateral cervical vagotomy was done in some experiments, usually at the beginning of the experiment.

Data for simultaneous right and left ventricular function curves were obtained in the following manner. The reservoir was lowered until the aortic pressure came down to 50 to 90 mm. Hg and then elevated in steps of 2 to 5 cm. at 30-second intervals until the left atrial pressure was 35 to 50 cm. H_2O. At this point high speed, full pressure tracings (50 mm. per second) were taken from both atria so as to ascertain whether obvious mitral or tricuspid regurgitation was present. Data for full ventricular function curves were obtained in 4 to 5 minutes and could be repeated frequently. Pressure and flow values were taken from the tracing at a point 30 seconds after each elevation of the reservoir. The stroke work of each ventricle in grammeters was calculated according to the following formula:

$$\frac{(cm.\ H_2O\ mean\ arterial\ pressure - cm.\ H_2O\ mean\ atrial\ pressure) \times stroke\ volume}{100}$$

Stroke volume in cubic centimeters was obtained by dividing systemic blood flow per minute by the heart rate. When either marked cardiac arrhythmias or regurgitation were found, the values were not used for the comparison of ventricular function curves.

Figure 1*A* shows a representative tracing of values obtained during a ventricular function run and the calculated right and left ventricular stroke work for each level of atrial pressure. Figure 1*B* shows the right and left ventricular function curves constructed from the data in figure 1*A*.

When the effect of a physiologic or pharmacologic intervention on myocardial contractility was studied, a control curve was obtained before the intervention and also after the removal of the intervention (figs. 4 and 5).

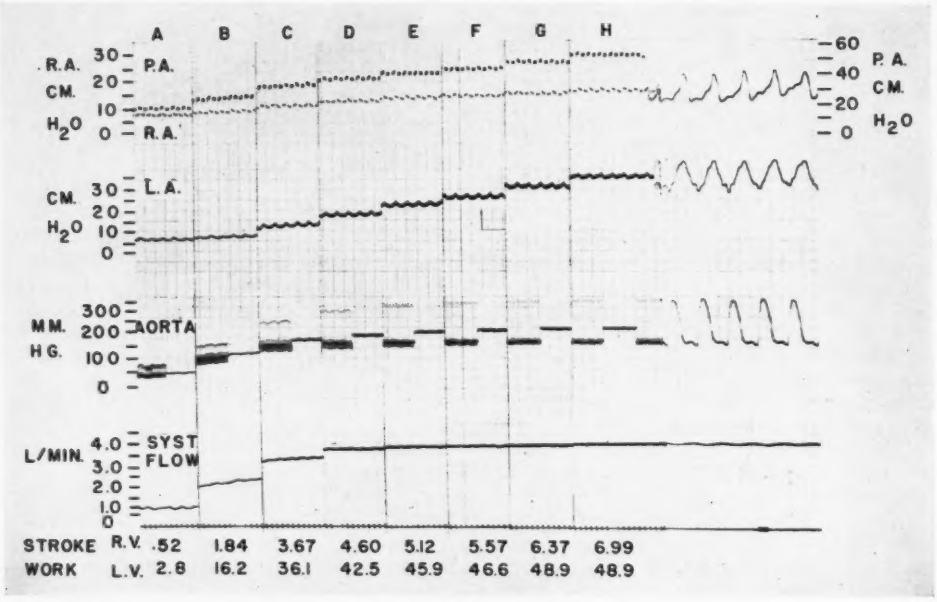
Evaluation of Method

1. The Use of Mean Atrial Pressure as an Index of Ventricular End Diastolic Pressures. (a) It is the authors' opinion that, at high heart rates, the precise determination of ventricular end-diastolic pressures is difficult to obtain consistently with the catheter technique. (b) The use of mean atrial

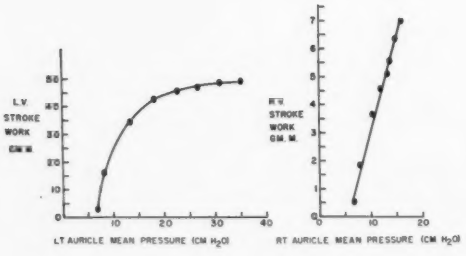
* The authors gratefully acknowledge the assistance of David M. Potter, Potter Aeronautical Company, Newark, N. J.

† Expandex supplied through the courtesy of Mr. Jerome Martin of Commercial Solvents Corporation, New York City.

* Supplied through the courtesy of Dr. Elmer L. Sevringhaus, Hoffmann-LaRoche, Nutley, N. J.



A



B

FIG. 1. Exper. 53. Dog weight: 23.6 Kg. Heart weight: 190 Gm. Pericardium open. Vagi intact. Reservoir connected to left atrium. (*A*) Tracing of pressures in pulmonary artery (P. A.), right atrium (R. A.), left atrium (L. A.) and aorta. Syst. Flow = Cardiac output minus coronary flow. Pressures in P. A., R. A., and L. A. are electrically integrated mean pressures; full R. A. and L. A. pulse pressures at the right. Aortic pressures are intermittently full and mean pressures; P. A. pressure scale at right, others at left. At the bottom are the calculated stroke work values of each ventricle at the various filling pressure levels. Time signal = 1 second. The reservoir was elevated at one-half minute intervals, the results of which are shown in B, C, D, E, F, G and H. (*B*) Left and right ventricular function curves plotted from the data in figure 1*A*.

pressures yields consistently reproducible ventricular function curves. (c) The correlation between mean atrial pressures and end-diastolic ventricular pressures was satisfactorily close in the low and medium ranges. The errors encountered at high filling pressures do not change the shape of the curve appreciably since in that range a moderate change in filling pressure does not significantly alter stroke work (figs. 1, 2, 4, 5, 6). (d) Another advantage of atrial over ventricular pressure recording is that, by the use of full atrial pulse contours, the presence of obvious tricuspid or mitral regurgitation may be detected. Ventricular recording does not afford this opportunity.

2. Accuracy of Flowmeter. The Electroturbinometer baseline is steady and its calibration is not affected by wide variations of blood viscosity or temperature. The correlation factor on blood calibrations with pulsating flow is 0.99.[14] The meter was calibrated after each experiment even though its calibration remained the same from month to month.

3. The Acceleration Fraction of Ventricular Stroke Work. In three experiments the kinetic component of the left ventricle stroke work was calculated during a ventricular function run. The following formula[21, 22] was used: $W_a = \frac{MV^2}{2g}$, in which W_a is acceleratio

work expressed in gram-meters, M is mass of blood per stroke in grams, and g is 9.81 M. per second^2. V is the mean ejection velocity in meters per second, and is calculated from the formula:

$$V = \frac{\textit{stroke volume in cc.}}{\textit{cross sectional area of root of aorta} \times (E) \times 100}$$

(E) is the systolic ejection time obtained from high speed aortic pressure tracings. The aortic cross-sectional area values were calculated from measured aortic circumferences obtained post mortem over the range of intra-aortic pressures encountered during the ventricular function run.

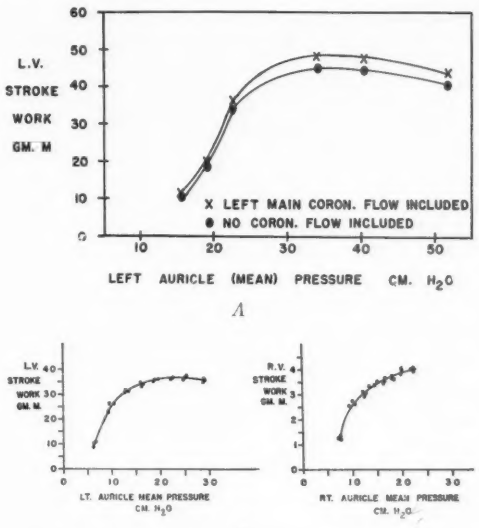
It was found that the acceleration component of left ventricular work during the entire ventricular function curve was less than 1 per cent of the total stroke work values obtained under the conditions of our experiment. This is in agreement with Remington and Hamilton.[23] The acceleration component of ventricular stroke work was disregarded in the calculation of the curves presented in this communication.

4. The Coronary Flow Fraction of Cardiac Output. Utilizing technics described in detail in other communications,[17, 18] the left main coronary artery flow was also measured while obtaining ventricular function curves in some experiments. Figure 2*A* shows the similarity of the shape and the minor difference in height of the function curves obtained (a) with the coronary flow included in the stroke volume values, and (b) without the coronary flow included. The subsequent ventricular curves shown do not include coronary flow in the calculation of stroke volume except for the curves shown in figure 4.

5. Equilibrium State. In order to ascertain whether equilibrium had been achieved 30 seconds after each elevation of the reservoir, two experiments were performed in which the atrial reservoir was raised at two-minute intervals instead of the usual 30-second intervals. Stroke work values were calculated and plotted against atrial pressure values at one-half minute, one minute and two minutes after each elevation of the reservoir. The result, shown in figure 2*B*, demonstrates that 30 seconds after any given elevation of the atrial reservoir, ventricular stroke work has reached its new level.

Results

More than 300 simultaneous right and left ventricular function curves have been obtained. Figure 1*B* shows ventricular function curves constructed from the data in figure 1*A*. It should be emphasized that left ventricle stroke work values are plotted against left atrial mean pressures, and right ventricle stroke work values against right atrial mean pressures.



A

B

FIG. 2. (*A*) Exper. 43. Comparison of left ventricle function curves with and without left main coronary artery flow included in the stroke work calculation. Dog weight: 18.4 Kg. Heart weight: 140 Gm. Pericardium open. Vagotomized. Reservoir connected to right atrium. (*B*) Exper. 49. Comparison of ventricular function curves obtained by calculating from values obtained one-half minute (dots), one minute (crosses) and two minutes (circles) after each elevation of the reservoir. Dog weight: 16.2 Kg. Heart weight: 170 Gm. Pericardium intact. Vagi intact. Reservoir connected to left atrium.

1. The Shape of the Ventricular Function Curves

The curves showed an initial steep rise at low filling pressures and then flattened off to a plateau with little or no decline even at high filling pressures. In our experiments this plateau always appeared in the left ventricular work curve. On the right, the shape of the curve was often as shown in figures 1*B* and 4, but not infrequently it was as shown in figures 2*B* and 6.

A descending limb, that is, a fall in stroke work at high filling pressures (50 cm. H_2O), did not occur in a normal heart with an intact pericardium. This is at variance with the classically conceived Starling curve which involves a pronounced descending limb at higher rates of "venous inflow."[11, 8, 12, 13, 41] In

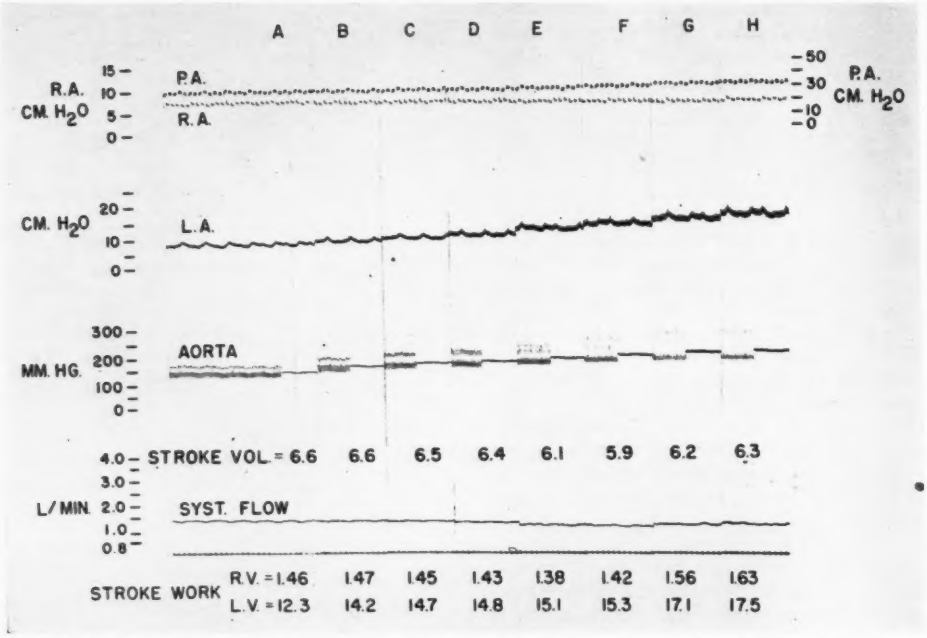


FIG. 3. Exper. 80. Effect of stepwise increase in aortic resistance (screw-clamp). Symbols same as those in figure 1A. Dog weight: 26.5 Kg. Heart wt.: 200 Gm. Pericardium open. Vagotomized. Aortic resistance increased at one minute intervals from A through H. Note rise in left atrial pressure which parallels rise in left ventricular stroke work, whereas right atrial pressure did not rise. Note also that a rise in stroke volume did not accompany the rise in left atrial pressure. See text.

our experience the descending limb was almost never on the right and on the left only under special circumstances; namely, the following: (A) when left main coronary artery flow is restricted (fig. 4); (B) in the presence of severe anemia[20]; (C) occasionally if the pericardium is widely open; when this *apparent* descending limb occurs there is suggestive evidence of ventriculo-auricular regurgitation[24]; (D) in the presence of pronounced cardiac irregularities (such as pulsus alternans) which sometimes appear at high filling pressures.

2. The Importance of Homolateral Correlation

It is seen in figure 1 that while right atrial pressure rose only 9 cm. H_2O throughout this function run, the left atrial pressure increased 28 cm. H_2O. This emphasizes the importance of relating right atrial pressure to right ventricle stroke work and left atrial pressure to left ventricle stroke work. Moreover, a change of pressure in one atrium is not always accompanied by a similar directional change in the other atrium. One such circumstance is illustrated in figure 3. A stepwise screw clamp constriction of the descending aorta was accompanied by stepwise increases of left atrial pressure from 9 to 17 cm. H_2O, while the right atrial pressure did not change significantly. The increases in left atrial pressures were accompanied by increases of left ventricle stroke work, while there was no significant change in right ventricle stroke work. It is apparent that attempts to correlate right atrial pressure and left ventricle stroke work under these circumstances may be misleading.[4]

3. The Importance of Correlating Filling Pressures with Work Instead of Stroke Volume or Cardiac Output

In figure 3 the stepwise increases in left atrial pressure were accompanied by stepwise increases of left ventricle stroke work

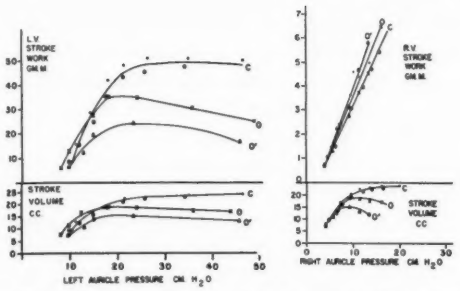
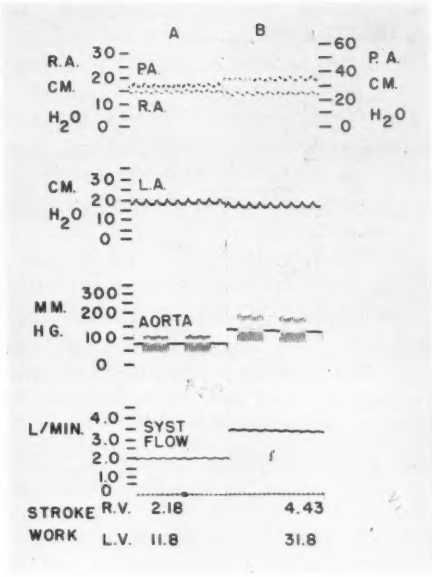

L.V. STROKE WORK GM. M.
R.V. STROKE WORK GM. M.
STROKE VOLUME CC.
STROKE VOLUME CC.
LEFT AURICLE PRESSURE CM. H2O
RIGHT AURICLE PRESSURE CM. H2O

FIG. 4. Exper. 72. The effect of restriction of left main coronary artery flow on right and left ventricular function curves. Dog weight: 16.8 Kg. Heart weight: 130 Gm. Pericardium open. Vagotomized. Reservoir connected to right atrium. Curve C = mean of control curves obtained before (dots) and after (circles) restriction of the left main coronary artery flow. Curve 0 = curve obtained during mild restriction of coronary flow. Curve 0′ = curve obtained during further restriction of flow. Note that during restriction of left main coronary artery flow there was: a) depression of the left ventricle function curve together with b) the appearance of a descending limb c) the occurrence of unilateral ventricular failure d) a misleading correlation between right atrial pressure and right ventricular stroke volume: i.e. right ventricular function was not depressed.

whereas stroke and minute output did not rise. It is obvious that the often used practice of correlating filling pressure with output[6-10, 12, 13, 25] may also be misleading.

Another physiologic circumstance under which the correlation between filling pressure and stroke volume may be misleading is shown in figure 4. After one set of control function curves was obtained (C, dots), the flow through the left main coronary artery was restricted by tightening a screw clamp on the tube feeding the coronary cannula. Ventricular function curves were obtained during mild (0) and moderate (0′) restriction of left coronary artery flow, and again after removal of the clamp (C, open circles). While the left ventricle was changing from the control to a depressed or "failure" curve, the right ventricle was unaffected, that is, did not show a depressed function curve. However, the plot of right atrial pressure against right ventricular *stroke volume* would give the impression that not only was the function of the right ventricle impaired but even that a descending limb was present. That such was not the case is clear



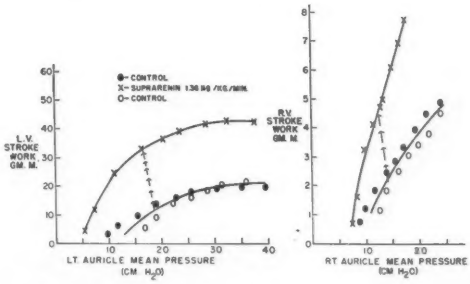


FIG. 5. Exper. 53. Same dog and symbols as shown in figure 1 after the myocardium was in failure. (*Upper figure*) Hemodynamic effects of a single intravenous injection of 1.17 μg per kilogram synthetic epinephrine (Suprarenin), made immediately after A. B is one-half minute later. Note the lower filling pressures and increased stroke work of both ventricles in B. (*Lower figure*) Comparison of simultaneously obtained left and right ventricular function curves before, during and 12 minutes after continuous infusion of the same agent.

Note that the effect of the single injection in the upper figure was simply to shift the ventricular performance from a point on the depressed function curve to a higher one as shown by the arrows. Figure 1 shows this dog's function curves before the heart went into failure.

from the right ventricle work plot. It was still doing as much work per unit of filling pressure, but more of this work was absorbed by the higher pulmonary artery pressures present.[17, 18]

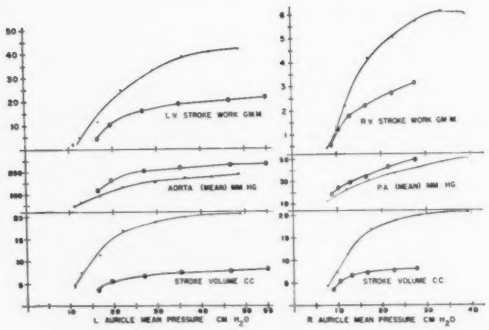

L.V. STROKE WORK GM.M.
R.V. STROKE WORK GM.M.
AORTA (MEAN) MM HG
P.A. (MEAN) MM HG
STROKE VOLUME CC
STROKE VOLUME CC
L. AURICLE MEAN PRESSURE CM. H2O
R. AURICLE MEAN PRESSURE CM H2O

FIG. 6. Exper. 24. Comparison of simultaneously obtained left and right ventricular function curves before and during increased aortic resistance. Pericardium intact. Dots, control curve. Circles, curve obtained while screw-clamp produced an increased aortic resistance. Dog weight: 18.2 Kg. Heart weight: 145 Gm. Vagotomized. Reservoir connected to right atrium.

The plot of right atrial pressure against cardiac output was similar to that shown for stroke volume since pulse rates were close to the same. The demonstrated occurrence of unilateral depression of left ventricular function (fig. 4) further emphasizes the importance of interpreting the function of each ventricle in terms of its own filling pressure.

4. The Importance of Distinguishing Between Apparent and Effective Filling Pressures

When the pressure around the ventricles was increased by the production of cardiac tamponade, the ventricular stroke work of both ventricles fell in spite of increased atrial pressures and thus the ventricular function curves during tamponade showed an *apparent* suppression.[26, 27] If, however, the *effective* filling pressure (pericardial pressure minus atrial pressure) was plotted against stroke work, no suppression of the ventricular function curves was observed. This is in accord with the view that the work of the ventricle is a function of diastolic fiber length[1, 28] and that this in turn is determined largely by the effective filling pressure.[29]

5. Family of Ventricular Function Curves

In the same dog, reproducible ventricular function curves were obtained while those factors which govern the response of the myocardium and vascular resistance remained constant. However, when these were significantly altered, many different types of curves could be obtained. Examples of such families of related curves are shown below.

A. *Effect of Epinephrine on the Ventricular Function Curve.* The upper part of figure 5 shows the hemodynamic effects of a single injection of synthetic epinephrine tartrate (Suprarenin). Prior to the injection (A) this dog exhibited evidence of myocardial failure, that is relatively little ventricular stroke work at elevated filling pressures. Thirty seconds after the injection of epinephrine (B), the stroke work of both ventricles was higher even though their filling pressures were lower. This apparent negation of the Starling relationship is clarified by the curves in the lower part of figure 5; that is, ventricular function curves before, during and after a *continuous* infusion of epinephrine. The curve during the epinephrine infusion is markedly higher than the curves obtained before and after it. The effect of the prior single injection of epinephrine was simply to shift the work performance of the ventricles from a point on the control function curve to a point on the epinephrine curve as indicated by the arrows. Another sympathomimetic amine, Aramine,* was similarly found to increase ventricular stroke work per unit of filling pressure.[30]

B. *Effect of Restricting Coronary Flow.* The restriction of left main coronary artery flow yielded progressively depressed left ventricular function curves the degree of which was a function of the restriction imposed (fig. 4).

C. *The Effect of Severe Anemia.* Moderate degrees of anemia did not lower the ventricular function curves significantly because of an observed increase in coronary flow. However, when the anemia became so severe that coronary vasodilation could no longer compensate for the lowered oxygen transport capacity of the blood, depression of the ventricular function curves occurred.[20] These were similar to those obtained by partial coronary occlusion seen in figure 4.

* Supplied through the courtesy of Dr. Karl Beyer Sharp & Dohme, West Point, Pa.

D. *The Effect of Aortic Constriction.* After obtaining a control curve, aortic resistance was increased by constriction of the aortic tubing. Figure 6 shows that during the curve with a high aortic resistance, the left ventricle produced less external stroke work at any given filling pressure. After removal of the aortic clamp, the curve was similar to the control. It will be noted that in this dog, with the pericardium intact, the right ventricle function curve was also suppressed when the aortic constriction was in place. This reflected or *apparent* lowering of the right ventricle curve shown in figure 6 did not occur in this dog after the removal of the pericardium, whereas the suppression on the left remained. The influence of the pericardium on cardiovascular hemodynamics is treated more fully in other communications.[24, 31]

The families of curves shown above demonstrate that certain factors which influence myocardial contractility and vascular resistance can alter the ventricular function curve of any given heart. However, if the full range of ventricular performance is again examined under the new conditions, a relationship between filling pressure and stroke work never fails to obtain.

Discussion

The examination of the relation between the "fiber length" in diastole and the "energy of contraction" presents two major technical problems in the mammalian heart. For, although the methods available at present allow a reasonably precise measurement of the *external* mechanical work performed by each ventricle, they do not measure the total energy liberated while doing this work. For example, it is likely that an appreciable portion of this energy is spent on isometric contraction, but that portion is not measurable as work in the physical sense. The relationship between myocardial oxygen consumption and ventricular work may vary significantly and therefore the former may not accurately represent the force of contraction.[32, 33]

Further, ventricular diastolic fiber length, to which the energy of contraction is apparently related, is also a determination which is extremely difficult to achieve in the *in vivo* mammalian heart. And, although the authors subscribe to this relationship as put forth by Starling,[1] neither he nor subsequent investigators achieved those measurements required to fully substantiate it. The cardio-oncometer does indicate changes in diastolic ventricular volumes and these do vary with diastolic fiber length. But this instrument measures the *sum* of right and left ventricular volumes and therefore cannot be used to determine the volume of either ventricle alone.[9] Disagreement has existed regarding whether it is the volume of the ventricle or the pressure in it which regulates the strength of the subsequent ventricular contraction.[1, 4, 28, 46, 47] For example, Starling's group came to the conclusion that it is the diastolic volume and not the filling pressure.[4] For, when they increased the outflow resistance to the *left* ventricle, its volume and thus the *sum* of the ventricular volumes increased, but, as might be expected, the right atrial pressure remained the same[4, 48] (See fig. 3). It seems to the authors that much of this debate is artificial. For, in any hollow viscus, an increase in its volume is accompanied by an increase in pressure, and these interdependent variables bear a constant relationship to each other unless a change in elasticity or tone occurs.

With these reasons in mind the form of analysis presented above was chosen; that is, the correlation of filling pressure with the external work produced. For, notwithstanding the basic limitations as regards energy measurements, this method does provide a rapid means of quantitating ventricular performance in terms of physiologically significant work. Thus, normal function, the deterioration of ventricular function and the effect of therapeutic maneuvers can be satisfactorily measured. Lastly, the data were gathered in terms of pressures and flows, determinations which are readily achieved in man. The measurement of ventricular volume in man is at present an uncertain one.

In this preparation it was frequently possible to make continuous output and work determinations and to obtain 20 simultaneous right and left ventricular function curves in a

single experimental animal. The work values in our preparation compare well with work values obtained in closed chest anesthetized dogs.[34] Unlike heart-lung preparations which are probably failing, this preparation still has normal or near normal metabolic support. The open-chest preparation has the advantage of avoiding the vagaries of intrapleural pressure measurements[35] and the consequent difficulty of precisely determining effective filling pressure. Attempts are being made, however, to achieve the type of measurements presented above in the unanesthetized, closed-chest dog for the purpose of other studies.*

Shape of the Ventricular Function Curves. As noted above, the ventricular function curve shows a steep initial rise which then flattens off to a plateau. The only available determinations of the pressure-volume relationship of the ventricle in the mammaliam heart are approximate because they were not done in the beating heart.[36] Nevertheless they reveal that in the low range, large volume (fiber length) increments produce only small increases in pressure. In the upper range, small volume increments produce large pressure increases. Considering this shape of the ventricular pressure-volume curve together with the shape of the ventricular function curves shown, it becomes likely that a plot of work against volume (or fiber length) would be closer to a straight line than either the ventricular function or the pressure-volume curves.[37]

The initial steep rise of the curve is of considerable importance. A rise of 1 cm. H_2O in atrial pressure may increase ventricular work by as much as 300 per cent. This emphasizes the necessity for precise measurements of the changes in effective filling pressure, especially in the normal heart.

The Absence of a Descending Limb on the Normal Ventricular Function Curve. The normal ventricular function curves presented above (with filling pressures as high as 55 cm. H_2O) differ from the classically conceived curves[1, 6, 12, 13, 38, 41] in that they show little or no descending limb. With the pericardium wide open, the stroke work values sometimes decreased at high filling pressures, but this phenomenon was attributable to regurgitation through the distended atrioventricular valves and not to a decrease of myocardial contractility. Frank observed this phenomenon in the frog heart and stressed its importance.[2] It has been demonstrated that the pericardium restrains extreme dilation of the heart[24, 31, 38, 39] and probably also prevents valvular regurgitation.[24] The classic Starling curve with a descending limb[1] was obtained in heart-lung preparations with the pericardium removed. But even in such a preparation, left atrial pressures of 40 cm. H_2O were occasionally reached without a fall in stroke work.[3] The findings of Lundin, namely, the extent to which a ventricular muscle strip can be stretched without a decrease in the force of contraction,[40] suggest the magnitude of increase in ventricular volume that would be required to produce a descending limb. And, as demonstrated above, a descending limb was not encountered in the normal heart even when the left ventricle was severely challenged by a high aortic resistance (fig. 6). A descending limb did occur when the metabolic support of the myocardium was compromised (fig. 4).[17, 18, 20]

Myocardial Failure. The shape of the normal ventricular function curve does not confirm the interpretation that cardiac failure may result merely from stretching the muscle fibers beyond that point where an increased filling pressure causes a decrease in cardiac work.[41, 42] We consider myocardial failure to be an alteration of the contractility of the myocardial fibers, resulting in a shift of the ventricle from a normal function curve to a depressed one. The increased filling pressures are thus not the cause of failure but a consequence of decreased myocardial contractility.

In regard to this general area McMichael, in 1952, stated "In the very near future we shall possibly abandon the vague term 'cardiac failure' and analyze all our cardiacs in terms of their altered dynamics."[43] With the exception of heart disease involving valvular insufficiency, it would appear that the use of ventricular function curves or portions thereof may bring this goal within reach.

Family of Ventricular Function Curves. In

* Ventricular function curves have recently been obtained in the closed-chest dog. The right and left ventricular function curves thus obtained are similar to those obtained in the open-chest preparation.

order to uphold the view of Frank and Starling it has been necessary to broaden this view with a spectrum or family of curves so as to have it encompass the observed phenomena. The idea of a family of Starling curves was first suggested to us by Dow in 1949.[44] In 1952 McMichael drew three theoretical plots of cardiac work against filling pressure representing the normal, the hypodynamic and the hypertrophied heart.[45] The theoretic curves presented by Youmans and Huckins[13] and by Lewis and coworkers[25] unfortunately plotted cardiac output or stroke volume against filling pressure. The data presented above and elsewhere[17, 18, 20, 24, 26, 27, 30, 31] substantially strengthen the view that a ventricle may describe many different ventricular function curves. These data also furnish examples of certain ways in which the curves may be altered (figs. 4, 5, 6).

A change in filling pressure in one direction accompanied by a change of ventricular work in the opposite direction (fig. 5) does not mean that the Frank-Starling relationship no longer obtains. It is still present but is shifted to another scale. This concept is helpful in understanding certain phenomena (for example, exercise, epinephrine) which, on the surface, are not in accord with Starling's law.

It is the view of Richards[8] and Hamilton[9] that the heart "has fallen back upon the Starling mechanism" only when other mechanisms for the regulation of "cardiac output" fail; that is, only the failing heart obeys Starling's Law. This interpretation overlooks the above demonstrated ability of the heart to operate on widely different Starling curves. The above data are consonant with the view of Youmans and Huckins: "It is an unfortunate choice of words to say that Starling's law is not operating when an increased cardiac output is associated with a decreased venous pressure. . . . In such cases the cardiac output is certainly less than it would be if the venous pressure were maintained. . . . "[13]

The question has reasonably been asked as to where the family of curves fits into our thinking about the circulation. For even if it is agreed that the Frank-Starling relationship does obtain in the intact mammalian organism, "of what use is this information if the myocardium can blithely skip from curve to curve?" Obviously, it is less convenient to have to deal with a family of curves rather than with a single curve. But it is much more convenient to deal with a family of curves than with a miscellaneous group of random values which do not fit any pattern at all. Further it is clear from the above that the ventricles do *not* "blithely skip from curve to curve" unless some influence of physiologic importance intervenes. This family of curves may therefore be helpful in understanding the nature of certain pathologic processes and, by the experimental use of such curves, factors which alter myocardial contractility may be more precisely determined.[17, 18, 20, 26, 27, 30, 49]

As expressed by Starling "the heart possesses in a high degree the power of adaptation to changed conditions which is the essential characteristic of living organisms."[21] In the authors' view the concept of a family of curves adds a third dimension to the Frank-Starling mechanism. This third dimensional adaptation is of importance not only in the responses of the normal organism but also in compensating for physiologic adversity.

The most important missing link in the chain of information derives from our present inability to determine changes in the pressure-volume relationship of each ventricle in diastole; that is, changes, if any, in ventricular tone or elasticity. If it were possible to correlate the family of ventricular function curves under varying conditions with simultaneously obtained ventricular pressure-volume curves, a comprehensive view of the physical determinants of cardiac action would be at hand.

As both Starling[1] and Frank[2] indicated, the law of the heart is little more than the application to cardiac muscle of what was already known about skeletal muscle by Blix in 1895[50] and Fick in 1882.[51] These four workers were, in one sense, anticipated by A. Waller in 1878 who grasped this matter when he stated that ". . . whenever the left ventricle is forced to work against a higher pressure it has to be filled abundantly and under higher pressure; this condition is fulfilled only if the blood runs in from the distended pulmonary veins at a higher pressure."*[52]

* Author's translation.

Conclusions

1. A preparation is described whereby it is possible to examine in the dog with a complete circulation the relationship between atrial pressures and external stroke work for the left and right ventricles simultaneously. Twenty combined ventricular function curves can frequently be obtained in one experiment.

2. In any given circulatory state there is a consistent relationship between atrial pressure and ventricular stroke work.

3. The ventricular function curve shows an initial steep rise, during which a 1 cm. H_2O increase in atrial pressure may increase the ventricular stroke work as much as 300 per cent. At high filling pressures the curve flattens off to a plateau.

4. A descending limb (decrease of ventricular work with increased effective filling pressure) does not occur in the normal dog heart but may occur in the heart with a compromised myocardium.

5. The above data confirm the opinion of Starr and his colleagues[53] namely, that stroke work is the proper value to consider in the analysis of ventricular performance. Whereas a consistent relationship was found between atrial pressure and the *stroke work* of the ventricle on the same side, such a relationship was not consistently found (a) between right atrial pressure and left ventricle stroke work, or vice versa; (b) between atrial pressure and stroke volume; or (c) between atrial pressure and cardiac output.

6. A significant alteration in the circulatory state (such as the injection of epinephrine, coronary artery constriction, severe anemia and increased aortic resistance) produced different ventricular function curves; in this new circulatory state, however, the relationship between atrial pressure and ventricular stroke work was again a consistent one.

7. It is felt that previous investigations which challenge the validity of the Frank-Starling relationship have been based on either (a) improperly attempted or misleading correlations, (b) failure to appreciate the steepness of the ventricular function curve in its lower ranges, and the importance of determining *effective* filling pressures, or (c) failure to appreciate that no single curve can adequately express the patterns of ventricular performance elicited when certain parameters of its work conditions are altered.

8. The demonstration of the family of Starling or ventricular function curves makes available a unifying concept on the basis of which changes in ventricular function can be more completely appreciated.

Sumario Español

1. Se describe una preparación en la cual es posible examinar en el pero con circulación completa la relación entre presión atrial y el trabajo externo por contracción cardíaca para el ventrículo izquierdo y derecho simultaneamente. Veinte curvas combinadas de función ventricular pueden frecuentemente ser obtenidas en un experimento.

2. En cualquier estado circulatorio dado hay una relación constante entre la presión atrial y el trabajo por contracción ventricular.

3. La curva de función ventricular muestra un ascenso rápido, durante el cual un aumento en presión atrial de 1 cm. de H_2O puede aumentar el trabajo por contracción ventricular por tanto como un 300 por ciento. A presiones de henchimiento altas la curva se aplana hasta formar una meseta.

4. Una porción descendente (decremento de trabajo ventricular con incremento en presión efectiva de henchimiento) no ocurre en el corazón del perro normal pero puede ocurrir en el corazón con un miocardio averiado.

5. Los datos arriba mencionados confirman la opinión de Starr y sus colegas, o sea, que el trabajo por contracción ventricular es el valor apropiado para considerar el análisis del funcionamiento ventricular. Aunque una relación consistente se encontró entre la presión atrial y el trabajo por contracción ventricular en el mismo lado, tal relación no fué consistentemente encontrada, (a) entre presión atrial derecha y trabajo por contracción ventricular izquierda, o vice versa; (b) entre presión atrial y volumen por contracción; o (c) entre presión atrial y producción cardíaca total.

6. Una alteración significativa en el estado circulatorio (como inyección de epinefrina, constricción coronaria, anemia severa y resis-

tencia aórtica aumentada) produjo curvas de función ventricular diferentes; en este nuevo estado circulatorio, sinembargo, la relación entre presión atrial y trabajo por contracción fué una vez más consistente.

7. Se cree que previas investigaciones que dudaban la validez de la relación de Frank-Starling habian sido basadas en una u otra de las siguientes razones; (a) correlaciones erróneas o impropiamente atentadas, (b) falta de apreciación del empinado de la curva de función ventricular en su esfera de actividad baja, y la importancia de la determinación de presiones de henchimiento, o (c) falta de apreciar el que una curva sencilla pueda expresar los patrones de funcionamiento ventricular producidos cuando ciertos parametros de sus condiciones de trabajo son alterados.

8. La demostración de la familia de curvas de Starling o de funcionamiento ventricular hace posible un concepto unificado a base de que cambios en función ventricular puedan ser más completamente apreciados.

REFERENCES

[1] STARLING, E. H.: The Linacre Lecture on the Law of the Heart. Given at Cambridge, 1915. London, Longmans, Green & Co., 1918.

[2] FRANK, O.: Zur Dynamik des Herzmuskels. Ztschr. Biol. **32:** 370, 1895.

[3] PATTERSON, S. W., AND STARLING, E. H.: On the mechanical factors which determine the output of the ventricles. J. Physiol. **48:** 357, 1914.

[4] —, PIPER, H., AND STARLING, E. H.: The regulation of the heart beat. J. Physiol. **48:** 465, 1914.

[5] BING, R. J.: The regulation of the dynamic and metabolic function of the human heart. Acta med. scandinav. **142** (Suppl. 266): 223, 1952.

[6] STEAD, E. A., AND WARREN, J. V.: Cardiac output in man: analysis of mechanisms varying cardiac output based on recent clinical studies. Arch. Int. Med. **80:** 237, 1947.

[7] WARREN, J. V., BRANNON, E. S., WEENS, H. S., AND STEAD, E. A.: Effect of increasing blood volume and right atrial pressure on circulation of normal subjects by intravenous infusions. Am. J. Med. **4:** 193, 1948.

[8] RICHARDS, D. W., JR.: Conditions of pressure and flow in the heart and great vessels in congestive heart failure. Acta med. scandinav. **128** (Suppl. 196): 116, 1947.

[9] HAMILTON, W. F.: The physiology of the cardiac output. The Lewis A. Connor Memorial Lecture. Circulation **8:** 527, 1953.

[10] SJÖSTRAND, T.: Volume and distribution of blood and their significance in regulating the circulation. Physiol. Rev. **33:** 202, 1953.

[11] RUSHMER, R. F., AND THAL, N.: Factors influencing stroke volume: a cinefluorographic study of angiocardiography. Am. J. Physiol. **168:** 509, 1952.

[12] HOWARTH, S., MCMICHAEL, J., AND SHARPEY-SCHAFER, E. P.: Effects of Venesection in Low Output Heart Failure. Clin. Sc. **6:** 41, 1946.

[13] YOUMANS, W. B., AND HUCKINS, A. R.: Hemodynamics in failure of the circulation. Springfield, Ill., Charles C Thomas, 1951.

[14] SARNOFF, S. J., AND BERGLUND, E.: The Potter electroturbinometer. An instrument for recording total systemic blood flow in the dog. Circulation Research **1:** 331, 1953.

[15] —, —, AND WAITHE, P. E.: The measurement of systemic blood flow. Proc. Soc. Exper. Biol. & Med. **79:** 414, 1952.

[16] SHIPLEY, R. E., AND WILSON, C.: An improved recording rotameter. Proc. Soc. Exper. Biol. & Med. **78:** 725, 1951.

[17] SARNOFF, S. J., CASE, R. B., AND BERGLUND, E.: Quantitative studies on the relationship between coronary flow and ventricular function by means of the Starling curve. Abstracts of Communications, XIX International Physiological Congress, Montreal, 1953, p. 728.

[18] CASE, R. B., BERGLUND, E., AND SARNOFF, S. J.: Ventricular function. II. Quantitative relationship between coronary flow and ventricular function with studies on unilateral failure. Circulation Research. In press.

[19] RAPPAPORT, M., AND SARNOFF, S. J.: An electronic multi-range, multi-channel, direct-writing pressure recorder. Federation Proc. **8:** 130, 1949.

[20] CASE, R. B., BERGLUND, E., AND SARNOFF, S. J.: Effect of graded acute anemia on coronary artery resistance and ventricular function. Federation Proc. **13:** 24, 1954.

[21] STARLING, E. H.: Some points in the pathology of heart disease. Lancet **1:** 569, 1897.

[22] EVANS, C. L., AND MATSUOKA, Y.: The effect of various mechanical conditions on the gaseous metabolism and efficiency of the mammalian heart. J. Physiol. **49:** 378, 1915.

[23] REMINGTON, J. W., AND HAMILTON, W. F.: The evaluation of the work of the heart. Am. J. Physiol. **150:** 292, 1947.

[24] BERGLUND, E., SARNOFF, S. J., AND ISAACS, J. P.: Ventricular function. IV. The role of the pericardium in the regulation of cardiovascular hemodynamics. Manuscript in preparation.

[25] LEWIS, B. M., HOUSSAY, H. E. J., HAYNES, F. W., AND DEXTER, L.: The dynamics of both right and left ventricles at rest and during exercise in patients with heart failure. Circulation Research **1:** 312, 1953.

[26] Isaacs, J. P., Berglund, E., and Sarnoff, S. J.: Acute cardiac tamponade studied by Starling curves. Federation Proc. **12:** 72, 1953.

[27] Isaacs, J. P., Berglund, E., and Sarnoff, S. J.: Ventricular function. III. The pathologic physiology of acute cardiac tamponade studied by means of ventricular function curves. In press.

[28] Katz, L. N.: The relation of initial volume and initial pressure to dynamics of the ventricular contraction. Am. J. Physiol. **87:** 348, 1928.

[29] McMichael, John: Heart. Ann. Rev. Physiol. **10:** 201, 1948.

[30] Sarnoff, S. J., Case, R. B., Berglund, E., and Sarnoff, L. C.: Ventricular function. V. The circulatory effects of aramine; mechanism of action of "vasopressor" drugs in cardiogenic shock. In press.

[31] Berglund, E., and Sarnoff, S. J.: Role of pericardium in the regulation of ventricular stroke work and output when the left ventricle is acutely challenged. Am. J. Physiol. **171:** 708, 1952.

[32] Starling, E. H., and Visscher, M. B.: Regulation of energy output of heart. J. Physiol. **62:** 243, 1927.

[33] Decherd, G., and Visscher, M. B.: Relative importance of performance of work and the initial fiber length in determining magnitude of energy liberation in heart. Am. J. Physiol. **103:** 400, 1933.

[34] Ferguson, T. B., Shadle, O. W., and Gregg, D. E.: Effect of blood and saline infusion on ventricular end diastolic pressure, stroke work, stroke volume, and cardiac output in the open and closed chest dog. Circulation Research **1:** 62, 1953.

[35] Wiggers, C. J., Levy, M. N., and Graham, G.: Regional intra-thoracic pressures and their bearing on calculation of effective venous pressures. Am. J. Physiol. **151:** 1, 1947.

[36] Isaacs, J. P., Carter, B. N., and Haller, J. A.: Experimental pericarditis: The pathologic physiology of constrictive pericarditis. Bull. Johns Hopkins Hosp. **90:** 259, 1952.

[37] —: Personal communication, 1952.

[38] Kuno, Yas: The significance of the pericardium. J. Physiol. **50:** 1, 1915.

[39] Wilson, J. A., and Meek, W. J.: Effect of the pericardium on cardiac distension as determined by X-ray. Am. J. Physiol. **82:** 34, 1927.

[40] Lundin, G.: Mechanical properties of cardiac muscle. Acta physiol. scandinav. **7:** Suppl. 20, 1944.

[41] Wiggers, C. J.: Circulatory Dynamics. Physiologic Studies. New York, Grune & Stratton, 1952. P. 44.

[42] Cournand, A.: A discussion of the concept of cardiac failure in the light of recent physiologic studies in man. Ann. Int. Med. **37:** 649, 1952.

[43] McMichael, J.: Some problems of heart failure. Acta med. scandinav. **142** (Suppl. 266): 701, 1952.

[44] Dow, J. W.: Unpublished observations, 1949.

[45] McMichael, J.: Dynamics of heart failure. Brit. M. J. **2:** 525, 578, 1952.

[46] Straub, H.: Dynamics des Sängetierherzens. Deutsches Arch. klin. Med. **115:** 531, 1914.

[47] —: Dynamics des Sängetierherzens. II. Dynamic des rechten Herzens. Deutsches Arch. klin. Med. **116:** 409, 1914.

[48] Berglund, E.: Ventricular function. VI. The relationship between left and right atrial pressures and its role in maintaining an equal output from the two ventricles. Manuscript in preparation.

[49] Krayer, O.: Versuche am Insuffizienten Herzen. Arch. exper. Path. u. Pharmakol. **162:** 1, 1931.

[50] Blix, M.: Die Länge und die Spannung des Muskels. Skandin. Arch. Physiol. **5:** 173, 1895.

[51] Fick, A.: Mechanische Arbeit und Warmeentwicklung bei der Muskelthätigheit. Leipzig, F. A. Brackhaus, 1882.

[52] Waller, A.: Die Spanning in den Vorhöfen des Herzens während der Reizung des Halsmarkes. Arch. Physiol. p. 525, 1878.

[53] Starr, I., Jr., Collins, L. H., and Wood, F. C.: Studies of the basal work and output of the heart in clinical conditions. J. Clin. Investigation **12:** 13, 1933.

A New Electrocardiographic Pattern Observed in Cerebrovascular Accidents

By G. E. Burch, M.D., Robert Meyers, M.D., and J. A. Abildskov, M.D.

An electrocardiographic pattern was encountered in patients with cerebrovascular accidents which consisted primarily of T waves of large amplitude and duration. Large U waves were often present which may fuse in part or entirely within the T wave. Because of the presence and fusion of the T and U waves, the prolonged Q-T interval associated with the pattern was most probably a Q-U interval.

DURING the past several years a distinctive electrocardiographic pattern has been observed in some patients with cerebrovascular accidents at the Charity Hospital at New Orleans. No reference to this association was found in the literature, although others have observed changes in the electrocardiograms of patients with cerebrovascular accidents.[1, 2, 3] Since no detailed description of the electrocardiographic pattern has been published, it is not possible to compare the pattern reported here with the isolated electrocardiographic changes noted by others.

In its most characteristic form, the pattern consists essentially of T waves of considerable amplitude and width and a long Q-T interval. Prolongation of the Q-T interval has been mentioned in association with cerebrovascular accidents,[3] but there has been no detailed description of the configuration of the associated T wave.

Method

No attempt has been made to review a large series of patients' records to ascertain the incidence of the electrocardiographic syndrome in cerebrovascular accidents, since electrocardiograms were not recorded on all patients with this clinical state. Furthermore, because of sudden or early death, this diagnosis could not always be definitely established. A review of the case histories of patients with a diagnosis of cerebral hemorrhage, subarachnoid hemorrhage or unclassified cerebrovascular accidents at Charity Hospital during the year 1950 revealed 10 electrocardiograms with the syndrome. In addition, tracings with this pattern from one private patient,* two patients observed in 1949, one in 1951 and three in 1952 were included, making a total of 17 electrocardiograms included in this report.

Table 1 summarizes certain clinical data concerning the patients whose electrocardiograms were studied. In most instances the diagnosis of cerebrovascular accident was established by clinical study alone. Hemorrhage was demonstrated by spinal puncture in 14 of the 17 patients, and in the remaining three parenchymal hemorrhage or arterial thrombosis (classified as C.V.A. in table 1) was diagnosed on the basis of neurologic manifestations.

Results

Results are summarized in table 1 and figures 1, 2 and 3.

Q-T Interval. The Q-T interval was prolonged in all electrocardiograms. The increase beyond normal duration, determined by Ashman's formula,[4] varied from 7 to 66 per cent, the mean being 29 per cent. The shortest Q-T interval was 0.44 second and the longest 0.80 second (table I).

T Wave. The typical T wave encountered in this electrocardiographic syndrome was a large wave with the same general configuration as found in association with myocardial ischemia (fig. 1). The T wave was usually negative in the standard and chest leads, although large

From the Department of Medicine, Tulane University School of Medicine and Charity Hospital of Louisiana at New Orleans, La.

Aided by a Public Health Service Research Grant (H-143), the Rowell A. Billups Fund for Research in Heart Disease, and the Mrs. E. J. Caire Fund for Research in Heart Disease.

* We are indebted to Dr. Arthur H. Steele of Paw Paw, Michigan for the use of this patient's electrocardiogram.

TABLE 1.—*Pertinent Clinical and Electrocardiographic Data*

Patient No.	Age (yrs.)	Sex	Diagnosis	Interval Before 1st ECG	Duration Q-T Interval (sec.)	Normal Q-T Interval (sec.)	% Increase	U Wave
1	78	M	Cerebral hemorrhage	—	0.80	0.48	66	Not prominent
2	79	M	Cerebral hemorrhage	24 hours	0.44	0.37	19	V_1 and V_2
3	50	M	Cerebral hemorrhage	24 hours	0.60	0.48	25	V leads
4	47	M	Cerebral hemorrhage	24 hours	0.48	0.41	17	V_2
5	65	F	Cerebral hemorrhage	24 hours	0.46	0.40	15	Not prominent
6	63	F	Cerebral hemorrhage	7 days	0.52	0.34	53	Not prominent
7	74	F	Cerebral hemorrhage	24 hours	0.44	0.40	10	V_2–V_6
8	34	F	Subarachnoid hemorrhage	24 hours	0.48	0.36	33	Not prominent
9	58	M	Subarachnoid hemorrhage	24 hours	0.48	0.40	20	V leads
10	32	F	Subarachnoid hemorrhage	48 hours	0.48	0.44	9	V_2–V_6
11	43	F	Subarachnoid hemorrhage	24 hours	0.64	0.45	42	V_2
12	70	M	Subarachnoid hemorrhage	4 days	0.60	0.47	27	V_2
13	63	F	Subarachnoid hemorrhage	48 hours	0.62	0.38	63	Not prominent
14	71	F	Subarachnoid hemorrhage	72 hours	0.44	0.35	26	All leads
15	65	M	C.V.A.	24 hours	0.44	0.34	30	III and V_4
16	47	M	C.V.A.	48 hours	0.44	0.41	7	V_1
17	58	M	C.V.A.	72 hours	0.44	0.37	19	Not prominent

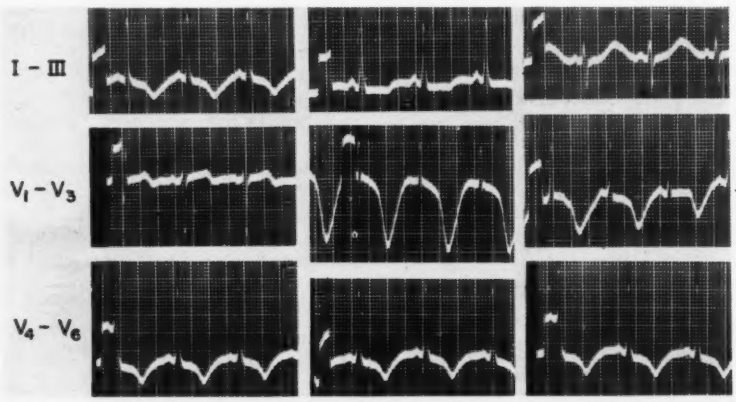


FIG. 1. Example of a typical electrocardiographic pattern associated with cerebrovascular accidents. This tracing was obtained from patient 16 listed in table 1.

positive T waves were encountered in the chest leads recorded from the right of the transition zone in lead V_3. Some of the widest and largest T waves seen in clinical electrocardiography were recorded in this syndrome (fig. 1). With improvement of the clinical state, the T waves reverted to a pattern dependent upon the underlying cardiac state, normal or abnormal (fig. 1*b* and *c*). In some cases, the T waves were so large that they occupied the entire interval between the R and P complexes (fig. 2); this was not always attributable to tachycardia, with associated shortening of the duration of electrical diastole.

U Wave. Some tracings contained large U waves (fig. 3) which were usually located within the T waves and were large and distinct in some instances but discernible with difficulty in others. It is possible, if not usual, that the U wave contributed to the deflections usually interpreted as T waves, but an adequate number of serial tracings was not available to clarify this point. Thus, because of the close association of the U wave with the T wave, the

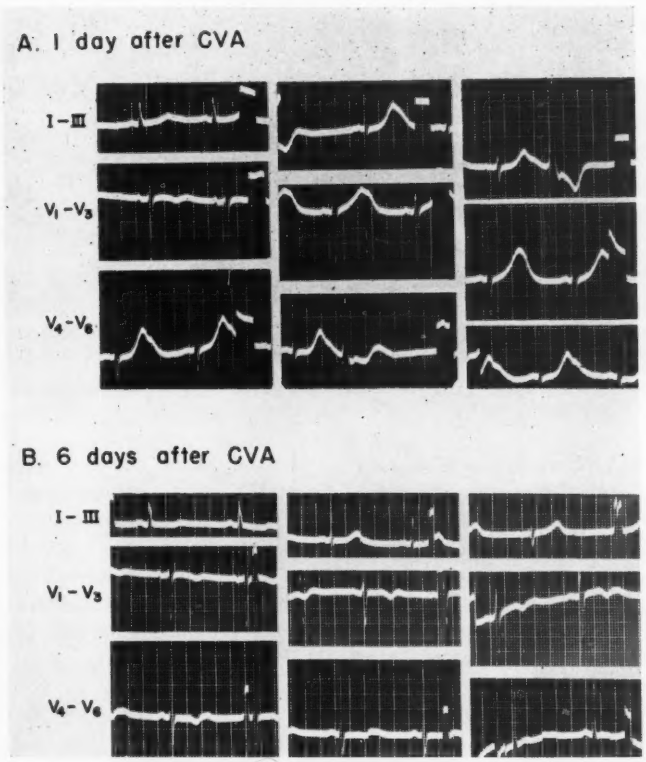


FIG. 2. Typical electrocardiographic patterns associated with cerebrovascular accidents. Tracing A was obtained from patient 12, 24 hours after a subarachnoid hemorrhage. Tracing B shows the disappearance of the electrocardiographic pattern six days after the hemorrhage in patient 12.

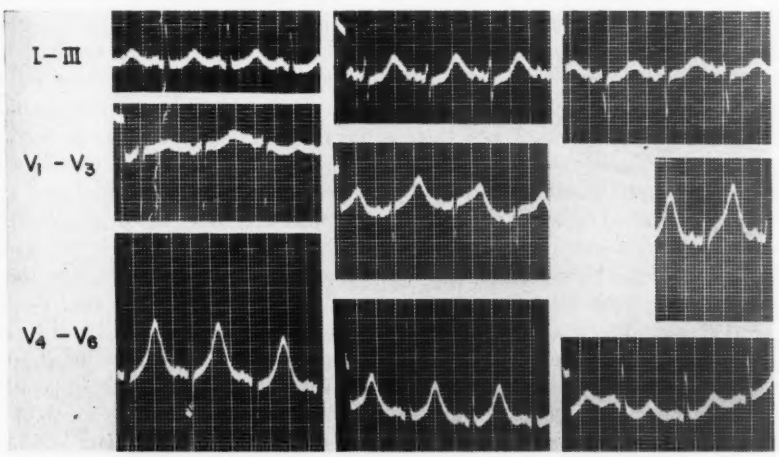


FIG. 3. Electrocardiographic tracing from patient 2 shows wide T waves occupying the entire interval between the T and P waves although the cardiac rate was 95 per minute.

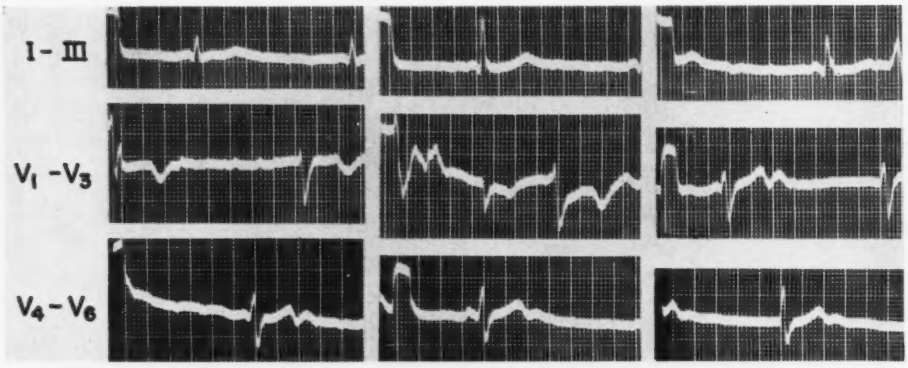


FIG. 4. Electrocardiographic tracing from patient 5 shows large U waves, especially prominent in leads V_2, V_4, V_5 and V_6.

long Q-T intervals shown in table 1 may actually be Q-U intervals. It is interesting that the T and U waves often exhibited configurations which resembled those accompanying electrolyte disturbances.

COMMENT

Four of the 17 electrocardiograms recorded for the patients in this series are presented. As in any biologic process, variations were considerable, the range remaining unknown. Whereas the typical pattern is easily identified, it may not be specific for cerebrovascular accidents and might occur in many forms of acute cerebral trauma, including physical injury to the brain. Detailed aspects of its incidence require further investigation.

The mechanism of the syndrome has not been studied. Opportunities were not available for adequate measurement of electrolytes in this series to determine whether or not the electrocardiographic changes were caused by disturbances in electrolyte metabolism. Such disturbances may conceivably have been at least partially responsible for the pattern, because acute cerebral injuries have been demonstrated to be associated with disturbances in electrolyte metabolism and because some of the electrocardiograms in this series resembled those encountered in patients with such disturbances. Changes in plasma potassium, sodium, pH and bicarbonate levels are known to produce alterations in T waves,[5, 6] and it is possible that other chemical, thermal or hemodynamic changes, as well as alterations in the autonomic nervous system associated with a cerebrovascular accident, may contribute to the electrocardiographic changes.

The most pronounced changes occurred in the subjects with subarachnoid hemorrhage, with the next most striking in those with cerebral hemorrhage. One patient had a moderate elevation in blood urea nitrogen (80 mg. per 100 cc.), but this declined promptly to 10 mg., and in three patients there was a slight elevation up to 29.4 mg. per 100 cc. Although none of the patients were diabetic, four had an elevation of blood glucose in association with the cerebrovascular accident.

The time at which the electrocardiographic changes occurred following the cerebrovascular accident could not be determined because the electrocardiograms were recorded within the first 24 hours of the cerebrovascular accident in nine patients, 24 to 48 hours in three patients, 48 to 72 hours in two patients, four to seven days in two patients, and the interval was not known in the other patient.

This electrocardiographic pattern was maintained for at least nine days in three patients and more than 11 days in one. Because of lack of adequate serial tracings and because of the death of some patients,[9] the duration of the electrocardiographic changes could not be determined from the data available. It is also interesting that five patients had bradycardia. As would be expected, T waves in the records of these patients were of greatest amplitude

and duration during the period of bradycardia. In no patient did the cardiac rate exceed 100 beats per minute. Because patients who have cerebrovascular accidents have often had chronic antecedent cardiac disease with abnormal electrocardiograms, the electrocardiographic patterns in tracing or serial tracings of any given patient were, of course, modified by such existing electrocardiographic abnormalities. All of these factors contributed to the variations encountered in the patterns.

Summary

A distinctive electrocardiographic pattern encountered in patients with cerebrovascular accidents consisting primarily of T waves of considerable amplitude and width, long Q-T interval, and large U waves has been described, but the mechanism responsible for the changes is not known.

Sumario Español

Un patrón electrocardiográfico se encontró en pacientes con accidentes cerebrovasculares, que consistió principalmente en ondas T de grande amplitud y duración. Ondas U grandes también fueron encontradas las cuales se fundían en parte o completamente con la onda T. Debido a la presencia y fusión de las ondas T y U, la prolongación del intérvalo Q-T asociado con este patrón fué probablemente debido al intérvalo Q-U.

REFERENCES

[1] Levine, H.: Non-specificity of the electrocardiogram associated with coronary artery disease. Am. J. Med. **15:** 344, 1953.

[2] Byer, E., Ashman, R., and Toth, L. A.: Electrocardiogram with large upright T waves and long Q-T intervals. Am. Heart J. **33:** 796, 1947.

[3] Lepechkin, E.: Modern Electrocardiography. Vol. I. Baltimore, Williams & Wilkins, 1951.

[4] Ashman, R., and Hull, E.: Eessentials of Electrocardiography. New York, Macmillan, 1941.

[5] Roberts, K. E., and Magida, M. G.: Electrocardiographic alterations produced by a decrease in plasma pH, bicarbonate and sodium as compared with those produced by an increase in potassium. Circulation Research **1:** 206, 1953.

[6] Magida, M. G., and Roberts, K. E.: Electrocardiographic alterations produced by an increase in plasma pH, bicarbonate and sodium as compared with those seen with a decrease in potassium. Circulation Research **1:** 214, 1953.

Frontal Plane Studies of Homogeneous Torso Models

By Ernest Frank, Ph.D., and Calvin F. Kay, M.D.

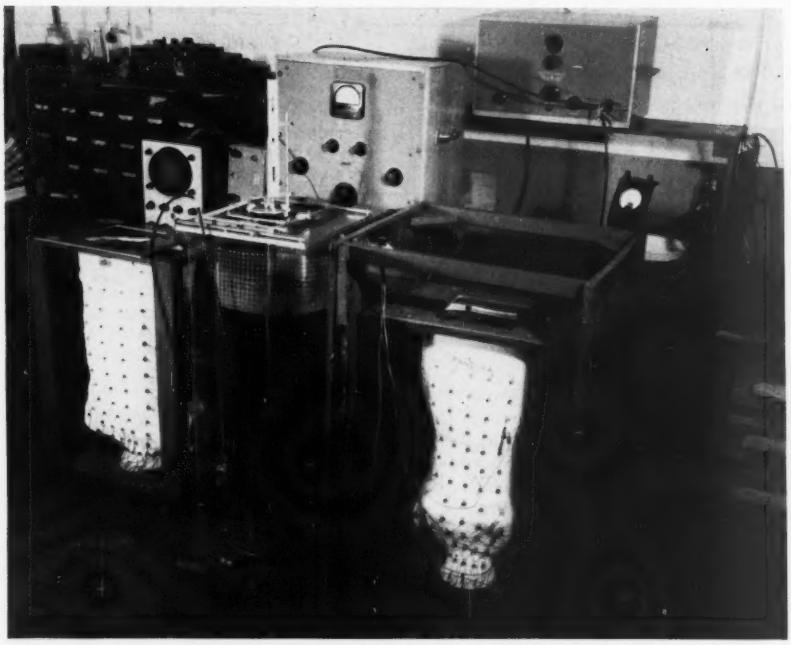
The accuracy of currently used vector methods of analysis of frontal-plane electrocardiograms and the behavior of the Wilson central-terminal voltage are investigated experimentally by means of an accurate unipolar voltage technic, using human torso models filled with a homogeneous conducting fluid in which is immersed a heart dipole. The errors entailed in the determination of the manifest heart vector from torso surface voltages by means of Einthoven's vector projection methods are found to be very sizable and strongly dependent upon the position of the heart dipole which is placed at various points within the heart volume in this investigation. Einthoven's angle α is found to depart from the actual heart-vector angle by -7 degrees to $+41$ degrees, at the instant when the manifest heart vector is a maximum, and the amplitude and shape of frontal-plane vector loops and limb leads are found to be considerably distorted, in many cases, as compared with the actual heart-dipole behavior. The Wilson central-terminal voltage is found to depart from its ideal value of zero by approximately 15 to 40 per cent of the maximum value of the manifest heart vector as seen in the frontal plane, in typical cases, and by more than 200 per cent in extreme cases. It is shown that the component of the dipole perpendicular to the frontal plane is not negligible in influencing the limb-electrode potentials. The results are found to be consistent within 10 per cent or better for a male and female torso differing widely in proportions and contour, except for an increase in the female torso voltages arising from its smaller physical dimensions. The results are presented principally in terms of the QRS complex, but the geometric triangle representation is given as are numerical coefficients which describe torso surface voltages.

DURING the past 40 years the use of the manifest heart vector[1] has become increasingly widespread in the interpretation of frontal-plane electrocardiograms. Furthermore, the use of the Wilson central terminal,[2] the potential of which depends upon electrode voltages in the frontal plane, has become commonplace. It has been known for years, however, that the mathematical expressions which are used to relate the limb leads to the manifest heart vector and which underlie the use of the Wilson central terminal are merely first-order approximations of the actual relationship between body-surface voltages and the electric currents generated by the heart.[3] The accuracy of the simplified theory which lies at the root of these widespread procedures has not been established quantitatively, and this has resulted in a diversity of opinion concerning their present worth and potential future promise. It has been the purpose of the experimental work described here on the human torso to investigate in quantitative terms the validity and accuracy of the analytic methods which are widely used in present day frontal-plane electrocardiography.

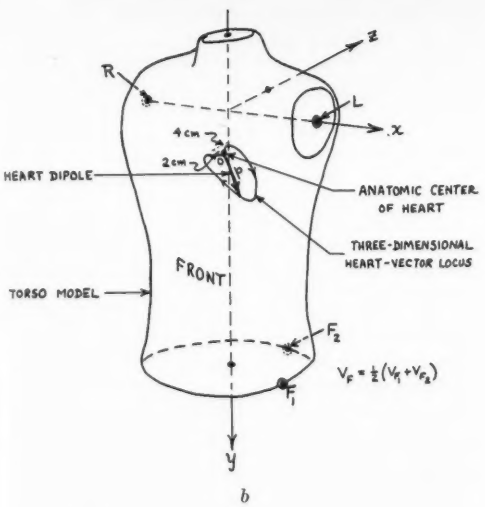
A group of rather stringent assumptions, loosely referred to as Einthoven's hypothesis, is implicit in the use of the manifest heart vector. These assumptions are that the human torso can be represented by a homogeneous, resistive, spherical conducting medium at the center of which is an electric current dipole representing the activity of the human heart. It is further assumed that the limb leads lie at the corners of an equilateral triangle whose apexes are on the surface of the sphere; the plane of the triangle is assumed to be parallel to the frontal plane and to contain the dipole. A mathematical analysis of this simplified representation leads to methods of vector projection in which the limb leads can be regarded as projections of the heart-dipole vector

From the Electromedical Group, Research Division, Moore School of Electrical Engineering, University of Pennsylvania, and the Edward B. Robinette Foundation, Medical Clinic, Hospital of the University of Pennsylvania, Philadelphia, Pa.

This investigation was supported in part by grants of the National Heart Institute, United States Public Health Service.



a



b

FIG. 1. Sketch of the male torso model in which arms, legs and head have been omitted, since a negligible amount of current penetrates these members. The directions of the coordinate axes are those which have been adopted tentatively as standard for vectocardiography. The x axis is directed from right to left (and is shown passing through the centers of the shoulders); the y axis is directed from head to foot (and is shown passing through the center of the neck); the z axis is directed from the chest toward the back (and is shown passing through the intersection of the x and y axes). The anatomic center of the heart is shown in the model sketch a distance 4 cm. in front of the x-y plane (frontal plane), 2 cm. to the left of the y-z plane (sagittal plane) and down from the x-z plane (transverse plane) to the level of the fifth intercostal space. Photographs of the male and female torso models are also shown. The torsos are mounted upside down in frameworks to permit greater flexibility in positioning the dipole than would be possible through the neck.

onto the sides of the equilateral triangle.[4] Moreover, as a consequence of these assumptions the Wilson central-terminal voltage is theoretically constant (zero) during the cardiac cycle.

In order to investigate in direct terms some of the shortcomings of the assumptions in the simplified theory cited above, accurate models of the human torso were constructed, filled with a homogeneous resistive fluid, and an electric dipole was inserted in various positions that are occupied in life by active heart muscle. Thus, the assumptions of a spherical shape, a centric dipole and an equilateral triangle were discarded. However, the assumption of a

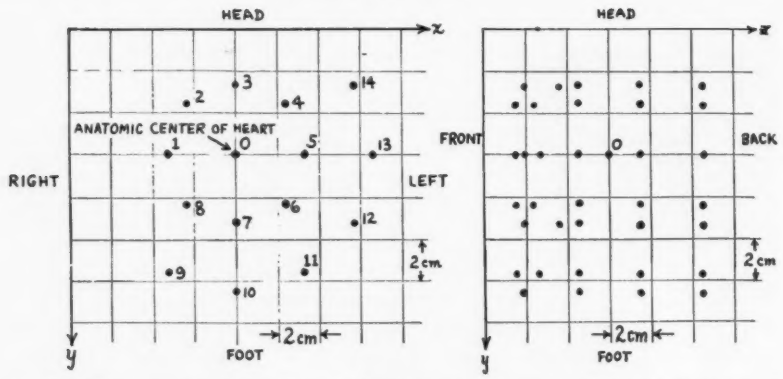


FIG. 2. Specification of typical points within the heart volume at which the dipole was fixed in position. The anatomic center of the heart is indicated by the point 0, also shown in figure 1. On the left, a plane parallel to the frontal plane shows that eight points numbered 1 through 8 form a circle around 0 with a radius of about 3.2 cm., while points 9 through 14 lie roughly on a circle with center at 0 and radius of about 6.5 cm. These latter points tend to favor the left ventricular region. Points 9 through 14 lie slightly outside the volume occupied by a normal heart.

The sagittal view on the right indicates that the frontal plane array of 14 dipole positions was repeated for three planes parallel to the frontal plane: 4.5 cm. behind 0, 1.5 cm. behind 0, and 1.5 cm. in front of 0. The fourth group of points are located, on the average, approximately 4 cm. in front of 0 and do not lie exactly on a plane because of mechanical interference between the dipole supporting rod and the front and chest of the torso model.

homogeneous, resistive medium was retained as was the dipole representation of the human heart. Although this model is still an idealized representation of the human system because of the last two assumptions, it nevertheless has served to establish some quantitative basis for the errors of the simplified theory. Furthermore, it is a three-dimensional volume conductor, which is more realistic than the two-dimensional models used in many other studies.[5-8]

METHOD

The experimental apparatus and method are described in detail in the appendixes and references cited there. Briefly, the torsos consisted of male and female, rigid, life-size, accurate, human body shapes (formed by molding to the human subject) with head, arms and legs omitted, as shown in figure 1. The insides of the torsos were coated with a thin waterproof lining of latex and filled with tap water. A finite dipole of sufficiently small size to yield dipole behavior at the surface of the torso was immersed by means of an insulated rod containing current leads; the dipole was capable of being accurately positioned and oriented over a wide range.* Current was fed to the dipole by means of a bridge arrangement (see fig. 13) which enabled true unipolar torso-surface voltages to be measured.[9] Unipolar voltages on the torso surface were measured, using water-tight pickup electrodes piercing the wall of the model at the shoulder centers, R and L (see fig. 1), and at two points of the left hip, F_1 and F_2. The potentials of the latter two points were always very nearly equal, as expected; their average was used to obtain the unipolar left-leg potential V_F as indicated in figure 1.

A typical experiment consisted of fixing the dipole position at a designated point within the heart volume and, in effect, causing the dipole to change its orientation and strength at that fixed position in accordance with estimates of normal heart-vector behavior during the QRS complex. The details of how this was actually accomplished are given in appendix II. The unipolar voltages were measured and the manifest heart vector was computed from them in accordance with the simplified theory, previously described, and compared with the known, assigned dipole variations. Appendix III gives the method of calculation. In addition, the Wilson central-terminal voltage was determined; this was made possible by the true unipolar nature of these measurements.

It can be seen from the above description that,

* A careful distinction is made between dipole orientation (axis direction) and dipole position (point of location). The term "position" has often been used in the literature to signify heart orientation which is rather confusing terminology.

contrary to the case in the human subject, the manifest heart vector determined from body-surface voltages could be compared with the actual heart vector that produced these voltages, since the dipole was deliberately inserted within the medium in an accurately-known, prescribed manner. Hence there was a direct check on the validity of the deductions made from the limb voltages.

The type of experiment described above was performed for a wide range of fixed dipole positions spread throughout the heart volume, 60 positions in the male torso and 53 positions in the female torso. A typical array of such points is given in figure 2 along with the number-coding used to designate the positions. The center point, designated by 0, was the anatomic center of the ventricular mass of the heart which in the models was located approximately 4 cm. in front of the x-y plane shown in figure 1, about 2 to 3 cm. to the left of the y-z plane and at about the level of the fifth intercostal space (see fig. 1). This point was determined by studying x-ray photographs of the subjects on whom the torsos were moulded.

At each dipole position, exactly the same variations in strength and orientation of the dipole were introduced for all experiments. These variations are given in figure 3 and were synthesized from human spatial vectorcardiograms of normal subjects.[10] It should be noted that, even though the frontal plane only was studied, the dipole was nevertheless caused to vary in three dimensions. It will be pointed out later that the dipole component perpendicular to the frontal plane, p_z, influences appreciably the limb leads despite the fact that this component has no effect whatever in the simplified theory of a centric dipole in a spherical conducting medium.

Results

It is not practical to present all of the details of the results because an enormous quantity of data was obtained. However, a representative sample of the findings will be given here.

Dipole in Anatomic Center of Heart. One of the marked discrepancies between the manifest heart vector derived from the limb leads and the actual heart vector can be seen in figure 4 in terms of frontal-plane vectorcardiograms. The solid loop is the projection of the actual heart dipole onto the frontal plane, that is, p_x versus p_y, and is ideally what should be derivable from the limb voltages. The other two loops are the loci of the manifest heart vector derived from measured limb voltages (using Einthoven's hypothesis) on the male and female torsos for the case of a dipole position in the anatomic center of the heart, point 0 of figure 1. It can be seen, in terms of Einthoven's angle α measured clockwise from the x axis, that when the true heart vector is a maximum its angle

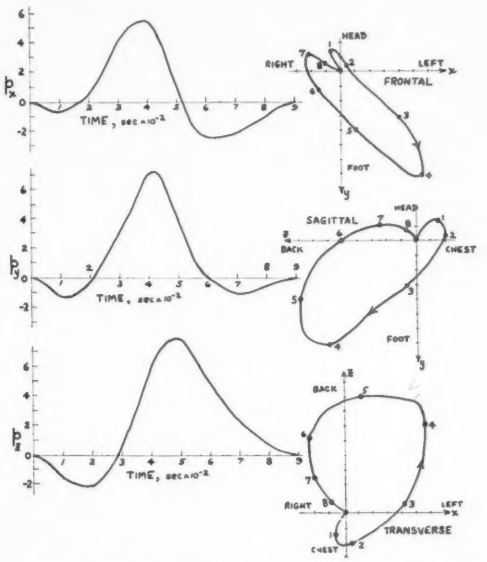


FIG. 3. Heart dipole strength and orientation time variations used at each of the positions of figure 2, in terms of the coordinate system of figure 1. These dipole variations were synthesized from three-dimensional vectorcardiograms of the QRS complex of normal subjects very kindly supplied by Dr. W. R. Milnor, Johns Hopkins University. At the left are shown the three rectangular projections, p_x, p_y and p_z, of the heart dipole moment, p, as a function of time which is in hundredths of seconds. On the right, three projections (any two of which define the heart vector uniquely) of the spatial heart-dipole variations are given; the frontal view is p_x versus p_y, the sagittal view is p_y versus p_z, the transverse view is p_x versus p_z. The units of p are relative.

The y component of the heart dipole, p_y, was deliberately reduced by a factor of roughly 2 from that in the records supplied by Dr. Milnor in anticipation of the result that in the torsos there is a marked tendency for an exaggeration of the head-to-foot component of the manifest heart vector as determined by ordinary methods. The introduction of this modification resulted in frontal-plane manifest heart vector loops, shown in figure 4, which resemble quite closely those in Dr. Milnor's records. However, as pointed out in the discussion and in appendix II, this is not a critical modification inasmuch as the essence of the results would be substantially the same for any reasonable heart-dipole variations that might be assumed.

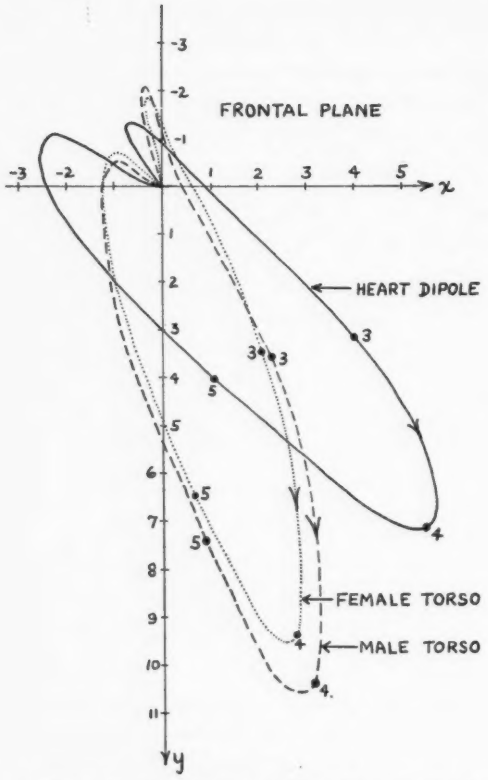


FIG. 4. Frontal-plane vectorcardiograms for the male and female torsos derived from the measured torso surface voltages for a dipole located in the anatomic center of the heart. The projection of the actual heart-dipole loop is also shown for comparison with the manifest heart vector. The heart-dipole loop is p_x vs. p_y in arbitrary units. The units of the manifest heart vector loops are relative, but the vector loop for the female torso is drawn to half the scale of the male loop. See text for discussion. The numbers 3, 4 and 5 on each of the loops indicate the time in hundredths of seconds.

is 52 degrees while the corresponding angle derived from limb leads was 75 degrees for both male and female torsos. The fact that the male and female torso angles agree indicates that the differences in torso shape for this dipole position are slight; however, the sizable shift in α from its true angle of 52 degrees to the apparent angle of 75 degrees, a difference of 23 degrees, indicates that the head-to-foot component of the heart dipole, p_y, tends to be exaggerated considerably in the homogeneous torso as compared with a homogeneous conducting sphere. Similar results have been found by other investigators.[8, 11] Perhaps this effect might be altered somewhat in the human subject since the resistivity of the human torso from the diaphragm down is thought to be considerably different from the rest of the body, but this point requires further investigation.

The relative magnitudes of the true heart vector and the manifest heart vector are of no concern in the present studies and have been discussed elsewhere.[22] However, the relative magnitudes of the male and female manifest heart vectors are significant and a rather interesting result was obtained which may not be immediately obvious from figure 4. The female vector loop given in figure 4 is drawn to half scale (for convenience) as compared with the male vector loop. The measured ratio of the maximum values of the manifest heart vectors is actually 1.8; that is, the maximum manifest heart vector in the female torso is 80 per cent greater than that in the male torso, and this was observed consistently for all dipole positions, despite the fact that the dipole current was held constant in all cases and the resistivity of the media in the two torsos was

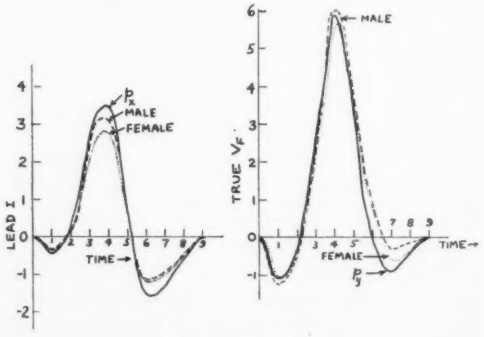


FIG. 5. At the left, lead $I = V_L - V_R$ for the male and female torsos is shown in terms of relative units of voltage for a dipole in the anatomic center of the heart, and compared with the right-to-left component of the dipole, p_x, with which they should agree ideally. At the right the unipolar voltages, V_F, are shown for the male and female torsos in terms of relative units of voltage for a dipole in the anatomic center of the heart, and compared with the head-to-foot dipole component, p_y, with which they should agree ideally. The female waveforms are drawn to half scale. The time scale is in hundredths of seconds

constantly controlled to be the same. This experimental result can be explained on the basis of female torso dimensions being considerably less than those of the male (see appendix I) and the fact that body-surface potentials depend upon inverse square and higher powers of the medium dimensions.

A comparison of leads I and V_F obtained in the torsos with p_x and p_y, respectively, is given in figure 5. The general shape of the waveforms is in fair agreement for this dipole position. However, it should be noted that the torso V_F leads are true unipolar voltages, unaffected by central-terminal variations. It can be seen in figure 6 that the Wilson central-terminal voltage variations are of magnitude comparable to lead I for a dipole located at point 0. The apparent V_F which would be observed with respect to the central terminal is also given in figure 6 for the case of the male torso where it can be seen, in this instance, that the effect of central-terminal variations is to deepen the S wave considerably. The maximum value of the central-terminal voltage in this case is equal to 16 per cent of the maximum value of the manifest heart vector (expressed in volts) for the male torso and 10 per cent for the female torso. The central-terminal voltage becomes much larger in proportion to the manifest heart vector for other dipole positions as will be shown later. In fact, the central-terminal voltage is quite near its smallest value for a dipole situated in the center of the heart.

Dipole Positional Changes in Planes Parallel to the Frontal Plane. As can be seen in figure 2, an array of dipole positions in a given plane parallel to the frontal plane (x-y plane) was employed, and this array was repeated for essentially four different planes spaced 3 cm. apart, two of which were in front of and two of which were behind the anatomic center of the heart. The trend of the behavior of torso surface voltages with dipole positional changes in any one of these planes was similar; therefore, the results will be presented here for a single plane located 1.5 cm. behind the anatomic center of the heart, which is representative.

Typical variations of lead I wave shapes are given in figure 7 for the male torso, which behaved similarly to the female torso. For

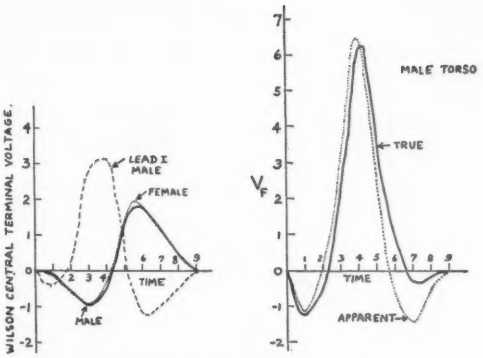


FIG. 6. At the left are shown the Wilson central-terminal voltages for the male and female torsos obtained with a dipole in the anatomic center of the heart. Lead I of the male torso for the same dipole position is also shown for comparison of relative magnitudes. The units of the Wilson central-terminal voltage are the same as those of lead I. The time is given in hundredths of seconds. An illustration of the effects of the Wilson central-terminal voltage on unipolar leads is given at the right. Here are shown for the male torso, and a dipole at 0, the true V_F which would be obtained in the absence of central-terminal variations and the apparent V_F which would actually be observed; the latter voltage is derived from the true V_F by subtracting the central-terminal voltage since the apparent V_F measured in electrocardiography is the potential difference between F and the central terminal.

dipole positions near the anatomic center of the heart, lead I can be seen to resemble p_x; however, the variations in both amplitude and shape are extreme as the dipole position shifts away from the heart center, particularly when it is in a region near the apex of the heart and especially at the left ventricular wall, point 13. It appears that the dipole position has a very pronounced effect on the wave shape inasmuch as it results in extreme effects in certain cases such as inverting the Q wave, reducing greatly the R wave, or deepening the S wave.

A group of typical frontal-plane vectorcardiograms is given in figure 8 for the male torso for the same dipole positions of figure 7. The behavior of the female torso was similar. Here the angle α at which the manifest heart vector is a maximum is seen to vary over the limits 62 degrees to 93 degrees, depending upon the dipole position, despite the fact that identical dipole variations are used at each position.

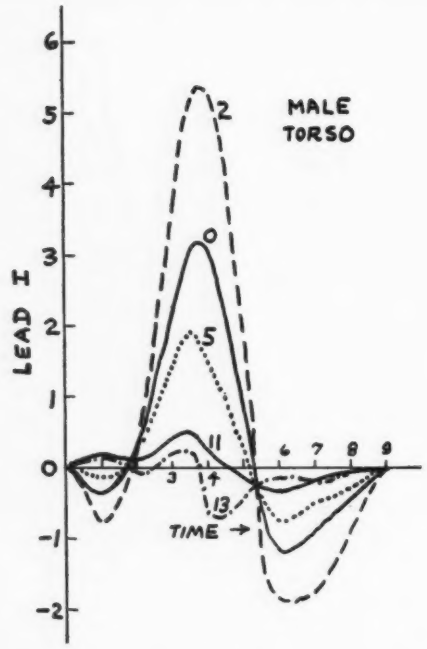


FIG. 7. Typical torso results for lead I are shown for several dipole positions on a plane parallel to the frontal plane which is located 1.5 cm. behind the anatomic center of the heart. All curves are to the same relative voltage scale and the time is in hundredths of seconds. The numbers on the curves refer to the dipole position points illustrated in figure 2.

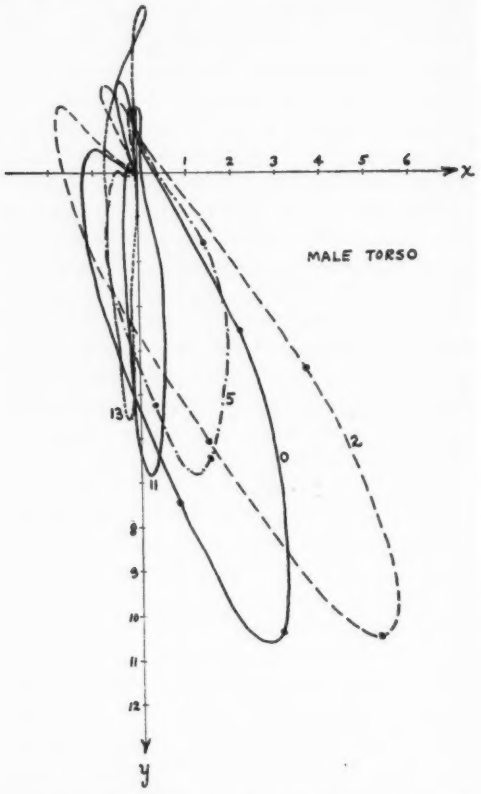


FIG. 8. Typical torso frontal-plane vectorcardiograms are shown for the same dipole positions of figure 7. The relative units shown are the same as those in figure 7. The numbers on the loops refer to the dipole position points illustrated in figure 2. All loops are traversed in the clockwise direction and the three points on some of them indicate successive instants of time at 0.03, 0.04 and 0.05 second.

Moreover, the relative amplitudes of the maximum value of the manifest heart vector vary by approximately 2 to 1 for these cases. Also, the shape of the vectorcardiogram shifts from a very thin loop in some cases to a fatter one in others. In a few extreme cases, not shown in figure 8, the direction of the maximum value of the manifest heart vector actually reversed by approximately 180 degrees.

Wilson central-terminal variations, shown in figure 9, also display wide variations in both magnitude and shape. Similar results were obtained for the female torso. These variations become more pronounced as the dipole position is shifted away from the heart center. In some cases the maximum value of the central-terminal voltage is as small as 6 per cent of the maximum value of the manifest heart vector, but in others it soars to values in excess of 200 per cent. Most of the maximum values are 40 per cent or less, however, and are the same order of magnitude as reported by other investigators.[12, 13]

The general trends shown by all of the data for dipole positional changes in planes parallel to the frontal plane may be summarized as follows:

(a) The maximum amplitude of the manifest heart vector tends to become diminished as the dipole position is shifted from R toward L by a typical factor of 1.5 to 2 over the range of positions used. On the other hand, the maxi-

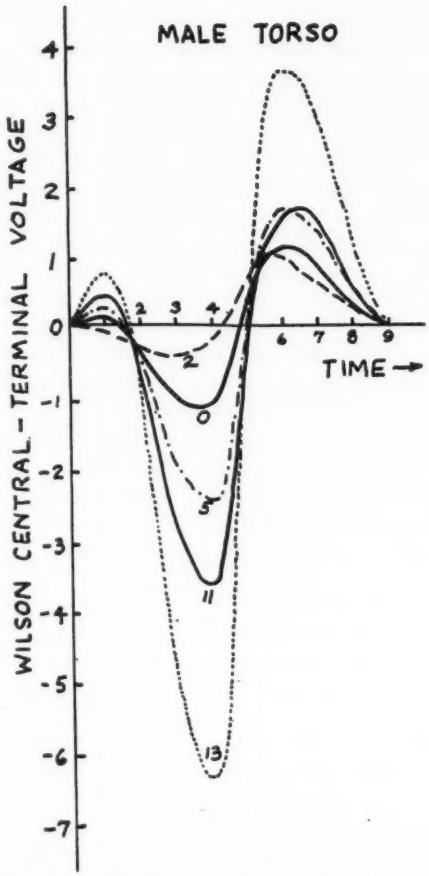


FIG. 9. Variations of the Wilson central-terminal voltage as a function of time in hundredths of seconds are shown for the male torso for the same dipole positions as figures 7 and 8. The relative units shown are the same as those in figures 7 and 8. The female torso data were very similar. The numbers on the curves refer to the dipole position points given in figure 2. The fact that the Wilson central-terminal voltages tend to follow a characteristic trend (initial rise, downward swing and upward overshoot at the end) is characteristic of this particular position plane. Different shapes are evidenced when the dipole is shifted toward the front or the back; for instance, in figure 6 there is no initial rise.

mum amplitude of the manifest heart vector remains substantially constant as the dipole position is shifted in the head-foot direction.

(b) Einthoven's angle α, at the instant the manifest heart vector is a maximum, tends to increase as the dipole is shifted from R toward L, typically by 10 degrees to 20 degrees over the range of positions used. This angle also tends to increase, typically by about 15 degrees, as the dipole is shifted from head toward foot over the range of positions employed.

(c) The Wilson central-terminal voltage tends to increase by 20 to 60 per cent of the maximum value of the corresponding manifest heart vector as the dipole is shifted from R toward L over the range of positions used. However, typical fluctuations are only about ± 5 per cent with the head-foot dipole positional changes employed.

Dipole Positional Changes in Front-to-Back Direction. The behavior with variations in dipole position in the front-to-back direction was similar in both torsos. The results for the male torso are given in the form of curves in figure 10 which cover position ranges from 4.5 cm. in

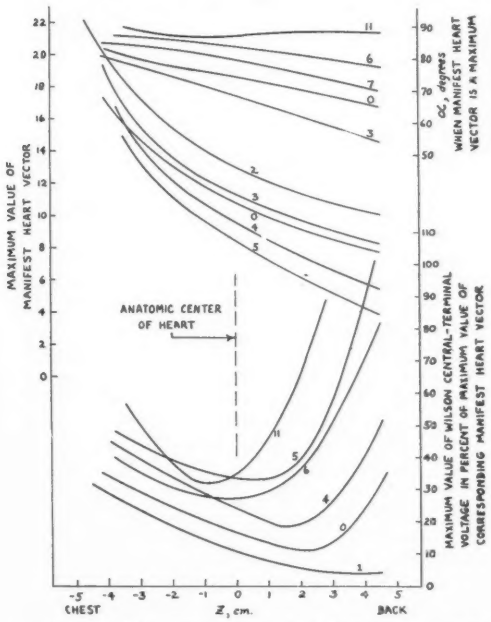

MAXIMUM VALUE OF MANIFEST HEART VECTOR
α, degrees WHEN MANIFEST HEART VECTOR IS A MAXIMUM
MAXIMUM VALUE OF WILSON CENTRAL-TERMINAL VOLTAGE IN PERCENT OF MAXIMUM VALUE OF CORRESPONDING MANIFEST HEART VECTOR
ANATOMIC CENTER OF HEART
CHEST
Z, cm.
BACK

FIG. 10. The dependence of Einthoven's angle α (upper curves), the maximum value of the manifest heart vector as seen in the frontal plane (middle curves), and the Wilson central-terminal voltage (lower curves) on the dipole position as it is shifted in the chest-to-back direction is illustrated for a group of representative dipole positions, indicated by the numbers on the curves. These results pertain to the male torso but a very similar trend was also observed for the female torso.

front of to 4.5 cm. behind the plane containing the anatomic center of the heart. The relative magnitude of the maximum value of the manifest heart vector is seen to decrease generally as the dipole is shifted toward the back. A typical change is in the ratio of approximately 2:1. The angle α at which the manifest heart vector is a maximum can also be seen to display a decreasing trend as the dipole is shifted backwards, a typical change in α for a designated frontal-plane dipole position is on the order of 20 degrees. The Wilson central-terminal variations are seen to pass through a minimum near the heart center, a typical minimum being about 15 to 20 per cent of the maximum value of the corresponding manifest heart vector. The maximun value of the central-terminal voltage generally becomes larger for dipole positions toward the back, reaching as high as 200 per cent in some cases and typically about 70 per cent, but for positions toward the chest it usually does not exceed 40 per cent.

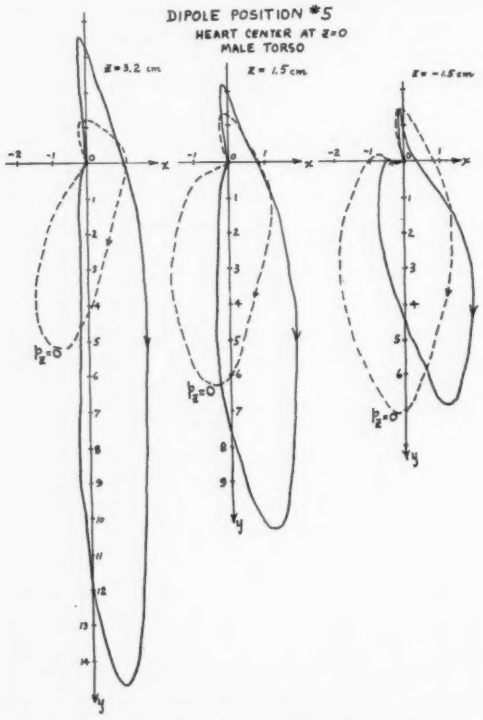


FIG. 11. Frontal-plane vectorcardiograms illustrating the effect of the chest-to-back component of the dipole, p_z, for dipole position 5 (see fig. 2) in the male torso. The solid loops are obtained with the three-dimensional dipole variations given in figure 3. The dashed loops result when the chest-to-back component of the dipole is made zero during the QRS complex but p_x and p_y are left unchanged. All loops are drawn to the same relative voltage scale. The left loops pertain to a plane containing dipole position 5 which is 3.2 cm. in front of the plane containing the anatomic center of the heart, point O. The center loops are for a plane 1.5 cm. in front of O, and the loops at the right are for a plane 1.5 cm. behind O.

These results are influenced by the fact that the true unipolar V_F was used rather than the apparent unipolar voltage obtained by subtracting from the true V_F the Wilson central-terminal voltage (see appendix III). Surprisingly enough, the apparent dependency of the body-surface voltages upon front-to-back dipole positional changes, which is strongly influenced by p_z, is reduced considerably because of the imperfections of the Wilson central terminal.

Effects of Front-to-Back Dipole Component. According to the simplified theory which underlies present vector-projection methods applied to the frontal-plane electrocardiogram, the dipole component which is perpendicular to the frontal plane has no influence whatever upon the voltages produced at R, L and F. Actually, this is true only if the dipole is centrically located in a symmetrical conducting medium, such as a sphere. In all other cases the dipole component perpendicular to the frontal plane will contribute to some extent to the voltages at electrodes which are in the frontal plane. In order to investigate in quantitative terms the extent of the effect of the front-to-back dipole component, a series of experiments in which p_z had been assigned definite values was repeated for certain selected points within the heart volume with all conditions the same except the dipole component in the front-to-back direction, p_z, was made zero; that is, the dipole variations were confined entirely to the frontal plane. An example of the results is given in figure 11 in terms of frontal-plane vectorcardiograms for three representative dipole positions in the male torso. It can be readily seen that the influence of the dipole component perpendicular to the frontal plane is very noticeable. However, as discussed in appendix

III, these results are dependent upon the method of treatment of the data, and are not necessarily as pronounced as shown in figure 11 when the compensating effects of the Wilson central-terminal imperfections are introduced. But under best conditions is it clear that the three-dimensional aspect of the dipole behavior cannot be ignored simply because the limb electrodes lie essentially in a plane. This can also be seen from the triangles in figure 12 whose planes are not parallel to the frontal plane.

Geometric Representation of Results. The geometric representation of limb leads in terms of scalene triangles, introduced by Burger and van Milaan,[14] is sometimes a useful way of expressing the relationship between the limb leads and the manifest heart vector. This representation can, of course, be applied to the results obtained here, in the form of a scalene triangle for each dipole position. The triangles which pertain to dipole position 0 are shown in figure 12 for the male and female torsos. The shape of these triangles would, of course, be influenced by inhomogeneities in the medium although the male torso relative values agree within 4 per cent of those obtained by Burger and van Milaan using an inhomogeneous torso.[11] The departure of these triangles from equilateral, the ideal used in simplified theory, gives some quantitative measure of the discrepancy between the manifest heart vector calculated from the equilateral triangle and that which would be calculated if the theory took into account the torso shape, the dipole position and the locations of the limb electrodes. In using these triangles to construct the scalar limb leads from the heart vector it is necessary to multiply the projection of the heart vector onto the side of the triangle in question by a scale factor that is proportional to the length of that side of the triangle. In other words, both the relative lengths of the triangle sides as well as their directions represent distortions from the simpler equilateral triangle in which the equal sides remove the need for scale factors. It is informative to note that these triangles are not parallel to the frontal plane, and this must also be so in the case of the human subject.

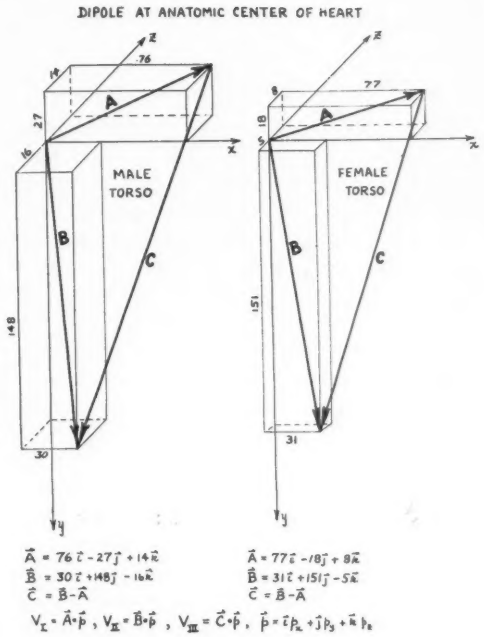

DIPOLE AT ANATOMIC CENTER OF HEART
MALE TORSO
FEMALE TORSO
A
B
C
x
y
z
$\vec{A} = 76\,\hat{\imath} - 27\,\hat{\jmath} + 14\,\hat{k}$
$\vec{B} = 30\,\hat{\imath} + 148\,\hat{\jmath} - 16\,\hat{k}$
$\vec{C} = \vec{B} - \vec{A}$
$\vec{A} = 77\,\hat{\imath} - 18\,\hat{\jmath} + 8\,\hat{k}$
$\vec{B} = 31\,\hat{\imath} + 151\,\hat{\jmath} - 5\,\hat{k}$
$\vec{C} = \vec{B} - \vec{A}$
$V_I = \vec{A} \cdot \vec{p}$, $V_{II} = \vec{B} \cdot \vec{p}$, $V_{III} = \vec{C} \cdot \vec{p}$, $\vec{p} = \hat{\imath} p_x + \hat{\jmath} p_y + \hat{k} p_z$

FIG. 12. Geometric representation of the male and female torso limb lead results for a dipole located in the anatomic center of the heart. The triangle is formed by three vectors, $\vec{A}$, $\vec{B}$ and $\vec{C}$, from which limb leads can be obtained by vector dot products with the dipole vector, $\vec{p}$, as indicated by the vector equations. The magnitudes of the vectors $\vec{A}$, $\vec{B}$ and $\vec{C}$ are 82, 152 and 184, respectively, for the male torso and 80, 154 and 176, respectively, for the female torso. The female torso numerical data have all been divided by a factor of 1.6 (determined from measurements at 192 different electrode positions on the torsos) in order to compensate for the difference in torso size. An attempt has been made to give a three-dimensional aspect to these triangles since their planes are not parallel to the frontal plane. In both cases the tip of the vectors $\vec{B}$ and $\vec{C}$ lie in front of the x-y plane while the tip of the vector $\vec{A}$ is located behind the x-y plane. The numbers on the sides of the rectangular solids correspond to the vector components.

Many of the results of this paper could be presented in the form of triangles, and the Wilson central-terminal voltage can also be represented geometrically as a vector directed from the dipole midpotential point to the median point of the limb-lead triangle.[15] But it is felt that the more commonly dealt with quantities involving the QRS complex convey

the results in a more direct, less abstract manner.

Discussion

It has been the purpose of the human-torso experimental work reported here to investigate the validity and accuracy of certain widely used methods of analysis of frontal-plane electrocardiograms. No claim is made that the torso models are faithful replicas of the human electrical system; rather they represent a relaxation of some of the assumptions that are implicit in currently used theories of electrocardiography. The assumptions of a homogeneous resistive medium and the dipole representation of the human heart have been adopted for experimental convenience with no intent of accepting these as necessarily accurately applicable to the human body. But these assumptions and more are inherent in most methods of analysis of the electrocardiogram. Even with these two idealizations concerning the medium and the heart generator, it has been demonstrated here that currently used methods of analysis of limb leads in terms of the projection of the manifest heart vector on the frontal plane result in very considerable distortion of the physical truth, particularly when the heart dipole is not in the anatomic center of the heart. Moreover, it has been shown that the Wilson central-terminal voltage variations are not negligible. In view of the results obtained it appears that heart-vector methods based essentially upon the simplified theory of Einthoven must be relegated to the category of a semiempirical mathematical device that is not accurately correlated to the electrical effects accompanying heart action in the human body. While these methods might serve a useful purpose in the interpretation of the electrocardiogram, they do not give an accurate account of the physical phenomena taking place within the body, and therefore are inherently limited.

An examination of appendix II will reveal that all of the results are contained essentially in a set of nine numerical coefficients for each dipole position. The use of a time-varying dipole, similar to presently accepted estimates of normal heart-vector behavior during the QRS complex, has been introduced in order to present the results in more palatable form in terms of quantities that are dealt with directly by the electrocardiographer, and to reduce the mathematical abstractness of these findings. The same coefficients determined here would be applicable for any assigned dipole variations whether P, QRS or T, and the trends of the results obtained would be essentially the same for a wide variety of dipole spatial loops. Therefore, restriction of the results to the QRS complex which emanates from a particular assigned dipole behavior should not be looked upon as a limitation of this work, but rather a device to make the results clearly understandable with a minimum of technical complexity.

It is believed that the position of the heart dipole does not remain stationary during the cardiac cycle.[16, 17, 18] Although the experiments reported here were conducted for fixed-position dipoles, this does not mean that variable-position effects have been ignored. Indeed, that is why a large number of different positions within the heart volume were used. The results here establish that the dipole positional changes are of considerable importance in determining the degree of departure of the manifest heart vector from the true heart vector and the extent to which the Wilson central-terminal voltage departs from zero, despite the fact that no experiments were performed in which the dipole position varied simultaneously with its orientation and moment. It is possible to make quantitative estimates of the consequences of a moving dipole from the data obtained, but this is a speculative matter because there is little information presently available concerning the path of the heart dipole during the QRS complex.

A theoretic analysis of frontal-plane quantities obtained in a homogeneous spherical resistive medium with an eccentric dipole confined to the frontal plane has been presented elsewhere.[19] The method, while entirely theoretic, was similar to that described here, but the simplicity of the medium boundary permitted mathematical calculations, and it was not necessary to resort to experiment. The results of the theoretic analysis, while not precisely the same as those obtained in the

torsos, largely because the front-to-back component of the dipole was always selected to be zero, indicate the order of magnitude of what was actually found in the present work. Thus, the rather marked departures from ideal obtained in the torsos were to be expected and, indeed, could be anticipated with fair accuracy based upon purely theoretical considerations.

It is clear that much more refined methods of analysis of human body surface voltages are necessary before electrocardiography can become an objective, precision, clinical tool. Indeed, presently used methods of analysis appear to be so approximate[15] that they might retard future progress in the understanding of the electrocardiogram because of misleading results obtained which depend upon factors not taken into account in the treatment of the data.

Summary

1. Experimental studies have been conducted for the purpose of investigating the Wilson central-terminal voltage and the accuracy and validity of the analysis of the frontal-plane electrocardiogram in terms of the manifest heart vector based essentially on Einthoven's hypothesis.

2. Experimental apparatus is described consisting of male and female torso models filled with a homogeneous conductor in which is immersed a current dipole, in conjunction with which is used an accurate unipolar voltage technic.

3. The errors entailed in the determination of the manifest heart vector from limb leads by means of simple vector projection methods are found to be very sizable and strongly dependent upon the position of the heart dipole.

4. Einthoven's angle is found to depart from the true heart-vector angle by as much as 41 degrees at the instant when the manifest heart vector is a maximum, and the amplitude and shape of frontal-plane vector loops and limb leads are found to be considerably distorted as compared with the actual dipole behavior.

5. The Wilson central-terminal voltage is found to depart from its ideal value of zero by approximately 15 to 40 per cent of the maximum value of the manifest heart vector as seen in the frontal plane, in typical cases, and by more than 200 per cent in extreme cases.

6. It is found that the component of the dipole perpendicular to the frontal plane is not negligible in influencing the limb electrode potentials, contrary to what would be predicted from the theory of a centric dipole in a homogeneous conducting sphere.

7. The results are found to be consistent within 10 per cent or better for a male and female torso differing widely in proportions and contour, except for an over-all increase in the female torso voltages, explainable because of its smaller dimensions.

8. The results which are presented in a variety of forms (QRS complex, numerical coefficients, and scalene triangles) are similar to those predicted from a theoretic analysis of an eccentric dipole in a homogeneous conducting sphere.

Acknowledgments

The painstaking care of Mr. Chauncey Elliot in the design and construction of the dipole and dipole positioning assembly is gratefully acknowledged. Many of the calculations were accurately performed by Mr. Robert S. Hager, the data were analyzed using Burger triangles by Mr. Jan A. Ruff, and Miss Mary Jane English helped with the experimental measurements. It is a pleasure to acknowledge their efforts as well as the stimulation provided by Dr. L. G. Thomson during the course of this study.

APPENDIX I

Experimental Apparatus

Torsos. Photographs of the two life-size torsos used in these studies are shown in figure 1. The male torso dimensions were: chest 40 inches, waist 32½ inches, hips 38 inches and the female dimensions were: bust 34 inches, waist 22½ inches, hips 33½ inches. They were constructed by molding a low melting point wax-impregnated cloth onto the human subject (Singer Sewing Machine Company dress-form technic) thereby giving an extremely faithful contour of the human figure. The neck and shoulders were sealed and the inside of the torsos were lined with several thin coats of latex. The latex was applied in liquid form using product GL-15C of the General Latex and Chemical Corporation, and air dried. The outside of the torso was bound with several layers of plaster bandage in order to provide rigidity under the pressure of the liquid with which the torso was filled. Approximately 200

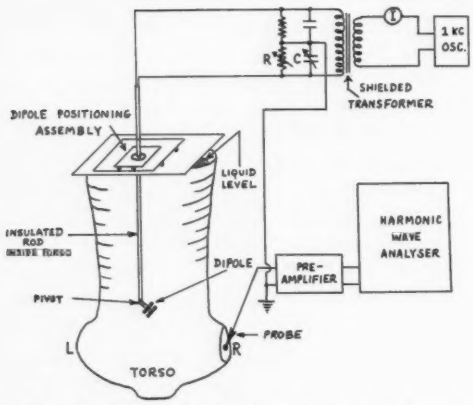


FIG. 13. Schematic drawing of the experimental arrangement for measuring true unipolar voltages on the torso models. The dipole is energized from a bridge circuit which is balanced by R and C, using an auxiliary cylindrical tank (shown in fig. 1) which establishes ground at the dipole midpotential. The dipole current is proportional to the reading of meter I in the transformer primary circuit. The dipole positioning assembly is located on a framework (see fig. 1) in which the torso is rigidly mounted. Good electrical shielding is used throughout: the oscillator, transformer and all leads are shielded and the torso model is housed in a copper screen cage as shown in figure 1.

watertight pickup electrodes were permanently installed over the surface of each torso. These consisted of 4:40 brass screws with neoprene and fiber washer seals. The models were mounted upside down as indicated in figure 1 and 13 so as to permit the dipole supporting rod to be inserted through the hip opening which permitted greater flexibility in positioning the dipole than would be possible through the neck. A plate with locating pins was mounted on a framework over the torso opening onto which the dipole positioning assembly, described below, fit snugly and with good reproducibility. The torsos were filled with tap water for convenience since the relative distribution of potential over the torso surface is independent of the resistivity of the homogeneous medium. The water used had a resistivity of about 2000 ohm-cm. Changes in resistivity owing to temperature changes of the water and accumulated impurities in the water were compensated for to an accuracy of better than 1 per cent by the technic described below.

Dipole. The finite dipole consisted of two 1 inch diameter nickel discs separated by a small $\frac{5}{16}$ inch insulating spacer. The dipole was pivoted at the end of a rigid insulated supporting rod of $\frac{3}{8}$ inch diameter. The finite dipole dimensions were selected to be small enough to yield mathematical dipole behavior at the torso surface and yet large enough to minimize the effects of electrode polarization, which become smaller as the electrode area is increased. Unpublished theoretic and experimental work indicated that at the medium boundary the finite dipole behavior departed by less than 1 per cent from that of a mathematical dipole. A pivot at the end of the supporting rod enabled the dipole orientation to be changed by ± 90 degrees. The supporting rod was clamped in a positioning assembly which permitted the rod to be twisted by known amounts about its axis and also to be displaced rectilinearly by means of a rolling track arrangement along the x and z axes shown in figure 1. The depth of immersion of the dipole was also adjustable and permitted the dipole to be positioned along the y-axis of figure 1.

Reference Potential. The dipole was energized from the bridge circuit shown in figure 13 using a frequency of 1000 cycles per second and a dipole current of 0.4 milliamperes, root-mean-square. The manner in which this arrangement enables true unipolar voltages to be measured without appreciable error owing to electrode polarization effects is described elsewhere.[9] The method, which is complicated by these troublesome effects, consisted of the following procedure:

(a) The finite dipole was placed along the axis of and midway between the end caps of a transparent, plexiglass circular cylindric tank (30 inches length and 7 inches radius) containing tap water of identical resistivity to that in the torso under measurement.

(b) The detector probe was connected to a pickup electrode located on a circle around the cylinder whose plane passed precisely through the geometric center of the finite dipole. The bridge circuit was adjusted for a null reading on the detector by means of the variables R and C in figure 13. This procedure established ground at the midpotential of the dipole (despite the existence of electrode polarization), which is the zero reference potential commonly used in electrocardiographic theory.

(c) The probe was then connected to a standard distant electrode on the cylinder wall and the dipole current was adjusted by setting the oscillator output control for a standard reading of 0.6 millivolts on the detector. The dipole current, measured indirectly in the transformer primary circuit, was noted and observed continuously for constancy throughout all of the measurements.

(d) The finite dipole was then transferred to the torso under test, certain standard electrode positions on the torso were checked immediately for reproducibility and drift, and the dipole-current constancy was checked.

(e) The probe was then connected to the torso electrodes R, L, F_1, and F_2, sequentially, and the torso unipolar voltages relative to ground (which remains at the dipole midpotential despite the transference of the dipole) were measured by means

TABLE 1.—*Torso Coefficients*

R L F	c_{1x} c_{1y} c_{1z} c_{2x} c_{2y} c_{2z} c_{3x} c_{3y} c_{3z}	$V_R = c_{1x}p_x + c_{1y}p_y + c_{1z}p_z$ $V_L = c_{2x}p_x + c_{2y}p_y + c_{2z}p_z$ $V_F = c_{3x}p_x + c_{3y}p_y + c_{3z}p_z$	
Dipole position	0	2	6
Male torso coefficients	−51 −57 27 25 −84 41 −21 91 11	−54 −54 45 40 −64 55 −7 90 26	−61 −60 42 −9 −96 57 −46 94 27

The equations for the unipolar voltages V_R, V_L and V_F are given in the upper right in terms of the coefficients c_{mn} which are constant for a fixed dipole position. A set of nine numerical coefficients is given in relative units for a few dipole positions in the male torso. These coefficients are arranged in accordance with the array in the upper left; for example, for dipole position 0, $c_{1y} = -57$ and $c_{3x} = -21$. The plane containing dipole positions 2 and 6 above was located 1.5 cm. in front of the anatomic center of the heart.

of the detector for various dipole positions and orientations.

The entire experimental procedure was repeated at least once for each dipole position studied with an interval of at least one week between repeat runs. In addition, during each test the dipole was periodically returned to the cylinder to check the stability of the reference potential setting. Under all conditions of these measurements, the drift in the reference potential was less than 1 per cent of the maximum boundary potential over a period of approximately six hours.

A great amount of time and effort have been expended in perfecting this reference potential technic as can be seen from other work which has been reported.[9, 20, 21] The frequency of 1000 cycles per second was carefully determined as the best compromise among system shielding difficulties, stray capacitance effects and electrode polarization disturbances, and variable frequency tests have been conducted over the range 150 cycles per second to 10,000 cycles per second to show that the potential distribution of 1000 cycles per second in the torsos is no different from that at lower frequencies. There are no measurable phase-shift effects at a frequency of 1000 cycles per second. The effects of wave form are eliminated by the use of the harmonic wave analyzer. The over-all experimental accuracy of the data obtained by this method was 5 per cent.

APPENDIX II

Torso Coefficients

The normal QRS dipole variations in orientation and moment shown in figure 3 were not actually introduced directly into the experimental procedure because of the enormous number of dipole orientations that would have to be employed. Instead, advantage was taken of the linear property of the medium in which the law of superposition is valid. Because the medium is linear, the potential differences between R, L and F and the dipole midpotential, V_R, V_L and V_F, respectively, can be expressed as a linear combination of the three rectangular components of the dipole moment, p_x, p_y and p_z, as shown in the three equations of table 1. The coefficients, c_{mn}, represent numbers which depend upon the location of the boundary pickup electrode, the torso shape, the characteristics of the medium and the dipole position. These coefficients are the same as those introduced by Burger and van Milaan in their model studies.[11, 14, 22, 23] The coefficients are constant provided the factors cited above do not vary. Consequently, if the coefficients are determined for a given dipole position, these same coefficients can be used for all values of variable, p_x, p_y and p_z, at that position, since the location of R, L or F does not change, the torso shape is rigid and the medium resistivity is stable. Thus, V_R, V_L and V_F can be obtained by calculations using the p_x, p_y and p_z functions of figure 2, and this is easier to do than the entirely experimental approach. For each dipole position a different set of coefficients pertains.

The actual experimental procedure consisted of determining the nine coefficients for each dipole position. This was done by first orienting the dipole entirely along the x axis such that p_y and p_z were zero and measuring the potentials at R, L and F (actually F_1 and F_2) which were then proportional to c_{1x}, c_{2x} and c_{3x}, respectively. The same procedure was repeated with the dipole oriented entirely along the y axis ($p_x = 0 = p_z$) to determine c_{1y}, c_{2y} and c_{3y}. Finally, using a z-oriented dipole ($p_x = 0 = p_y$) the remaining three coefficients were established. Each coefficient was determined by two independent measurements in which the dipole orientation was reversed by 180 degrees to reduce substantially the slight errors introduced by the presence of the rod support. With the set of nine coefficients determined for a given dipole position, the unipolar voltages, V_R, V_L and V_F, as a function of time were computed by means of the equations in table 1 using the dipole functions of figure 2. As an illustration the

coefficients for three dipole positions in the male torso are given in table 1. It can be seen that these coefficients depend markedly upon dipole position, but their interpretation may be more difficult than in terms of a variable heart vector and time varying torso surface voltages. The coefficients actually contain the essence of the experimental results. As pointed out in the discussion, the assigned dipole variations were used to minimize the mathematical obscurity of the findings. These coefficients were also used to determine the scalene triangles of figure 12. The Wilson central-terminal voltage was calculated from $\frac{1}{3}(V_R + V_L + V_F)$ and compared with directly measured values for the dipole orientations used experimentally.

To give an idea of the quantity of data obtained and the care with which these results have been determined, a total of over 5000 independent experimental determinations of the coefficients was made. These were made for 113 different dipole positions using four boundary electrodes with three coefficients for each surface electrode, and using a reversed dipole for two-thirds of the coefficients. Moreover, each determination was repeated at least once with equal care.

APPENDIX III

Method of Analysis

True unipolar data obtained in these studies has led to a problem which is believed to be novel in the field of electrocardiography, although similar problems have arisen in other fields. The existence of this problem creates a situation in which the end results are dependent upon which one of several alternative calculation methods is used. A method was selected in this work which is believed to convey a fair picture of the errors entailed in using simple vector-projection schemes, which has been the primary objective. However, if other methods are employed, different results are obtained.

In essence, the problem stems from the fact that the voltages at the surface of the torso (or human body) depend upon many more variables than are introduced in the simplified theory of a centric dipole in a homogeneous conducting sphere with an inscribed equilateral triangle. As obvious illustrations, torso voltages actually depend upon dipole position, but in the simplified theory the dipole position is fixed; or, again, torso voltages depend upon torso shape, but in the simplified theory the shape of the medium is fixed. These and other factors represent physical variables in the actual system which are suppressed in the idealized system. Therefore, when an attempt is made to treat the actual voltages by using the simplified theory, inconsistencies are bound to arise. As a specific illustration, it can be shown, for a centric dipole in a homogeneous conducting sphere with R, L and F at the apexes of an equilateral triangle, that the sum of the true unipolar voltages $V_R + V_L + V_F$ is zero.[4] However, in the actual system (torso or human) the sum of the true unipolar voltages is not zero*. This is, of course, a well known direct contradiction with simplified theory.

As a consequence of the supression of variables, the result obtained for the manifest heart vector depends upon the route by which it is calculated when true unipolar voltages whose sum is not zero are used. This is because the various alternative formulas that are available, all of which are consistent if $V_R + V_L + V_F = 0$, become inconsistent when the sum $V_R + V_L + V_F$ is not zero. As a specific illustration, it can be shown for the centric dipole in a sphere that the Einthoven angle α is given by a large number of forms, a few of which are

$$\tan \alpha = \frac{V_I}{\sqrt{3}\,V_F} = \frac{2(V_{II}/V_I)-1}{\sqrt{3}} = \frac{\sqrt{3}}{2(V_L/V_F)+1}$$

where these equations are self-consistent only if $V_R + V_L + V_F = 0$. However, if $V_R + V_L + V_F$ is not zero, the numerical value of tan α will be different depending upon which expression is used. This is merely an illustration; actually there are a half dozen more ways in which tan α can be expressed and calculated from true unipolar data, obtaining different results in each case.

Faced with this problem, to which there is no straightforward solution, it was decided to determine the frontal plane vectorcardiogram from the values of V_R, V_L and V_F by using $V_I = V_L - V_R$ and $\sqrt{3}\ V_F$, where V_F is the true unipolar voltage and not the potential difference between F and the central terminal. Of course, V_I was plotted along the x axis and $\sqrt{3}\ V_F$ along the y axis, as dictated by simple theory.[4] However, other methods of determining the vector loops would lead to different results, as pointed out previously. This method was selected, being based upon usual practice and intent in frontal-plane electrocardiography, although the electrocardiographer does not have the true unipolar voltage V_F available, and also because it gave a rough mean of various possible methods which were tried in the analysis of the experimental results.

Sumario Español

1. Estudios experimentales han sido conducidos con el propósito de investigar el voltaje central terminal de Wilson y la exactitud y precisión del analisis del electrocardiograma de

* The unipolar voltages employed on the human subject are not true unipolar voltages, but rather are potential differences from R, L and F, respectively, to the central terminal which is not at the dipole midpotential. These apparent unipolar voltages inevitably add up to zero[24].

plano frontal en términos del vector cardíaco manifiesto basado esencialmente en la hipotesis de Einthoven.

2. Aparato experimental se describe consistiendo de torsos masculinos y femeninos llenos de un conductor homogéneo en el cual se sumerge un dipolo de corriente, en conjunción al cual se usa una técnica precisa de voltaje unipolar.

3. Los errores vinculados a la determinación del vector cardíaco manifiesto de las derivaciones de las extremidades por sencillos métodos de proyección vectorial han sido hallados bastante grandes y fuertemente dependientes en la posición del dipolo cardíaco.

4. Se encontró que el ángulo de Einthoven se aparta del ángulo del vector cardíaco verdadero por tanto como 41 grados en el instante cuando el vector cardíaco manifiesto llega a su máximo y la amplitud y configuración de las ondas del vector de plano frontal y las derivaciones de las extremidades al compararse con el proceder del dipolo actual.

5. El voltaje central terminal de Wilson se encuentra desviar de su valor ideal de cero por aproximadamente un 15 a un 40 por ciento del valor máximo del vector cardíaco manifiesto como es observado en el plano frontal, en casos típicos, y por más de 200 por ciento en casos extremos.

6. Se encuentra que el componente de la perpendicular del dipolo al plano frontal no es insignificante en su influencia sobre el potencial de los electrodos de las extremidades, contrario a lo que se predeciría de la teoría de un dipolo céntrico en un esfera de conductividad homogénea.

7. Los resultados se hallan consistentes hasta un 10 por ciento o más para un torso masculino y femenino difiriendo grandemente en proporciones y contorno, excepto por un aumento total en el voltaje del torso femenino, explicable por sus dimensiones menores.

8. Los resultados que se presentan en una variedad de formas (complejos QRS, coeficientes numéricos y triángulos escalenos), son similares a aquellos pronosticados de un analisis teórico de un dipolo excéntrico en una esfera de conductividad homogénea.

REFERENCES

[1] Einthoven, W., Fahr, G., and de Waart, A.: Über die Richtung und die Manifeste Grösse der Potentialschwankungen im Menschlichen Herzen und über den Einfluss der Herzlage auf die Form des Elektrokardiogramme. Arch. ges. physiol. **150:** 275, 1913.

[2] Wilson, F. N., Johnston, F. D., Macleod, A. G., and Barker, P. S.: Electrocardiograms that represent the potential variations of a single electrode. Am. Heart J. **9:** 447, 1934.

[3] —, —, Rosenbaum, F. F., and Barker, P. S.: On Einthoven's triangle, the theory of unipolar electrocardiographic leads and the interpretation of the precordial electrocardiogram. Am. Heart J. **32:** 277, 1946.

[4] Frank, E.: "The Elements of Electrocardiographic Theory", Tr. Am. Inst. Elect. Engrs. (Communications and Electronics). P. 125, May, 1953.

[5] Katz, L. N., Jochim, K., and Goldman, A.: The effect of an injured area on the electrical field of the heart based on experiments with models. Am. J. Physiol. **137:** 779, 1942.

[6] Taccardi, B.: Measurements of errors of vectorcardiography as function of the leads used. Acta cardiol. **6:** 219, 1951.

[7] McFee, R., Stow, R. M., and Johnston, F. D.: Graphic representation of electrocardiographic leads by means of fluid mappers. Circulation **6:** 21, 1952.

[8] Brody, D. A., and Romans, W. E.: A model which demonstrates the quantitative relationship between the electromotive forces of the heart and the extremity leads. Am. Heart J. **45:** 263, 1953.

[9] Frank, E., and Kay, C. F.: A reference potential for unipolar electrocardiographic measurements on models. Am. Heart J. **46:** 195, 1953.

[10] Milnor, W. R.: Private communication. Johns Hopkins Hospital, Baltimore, Md.

[11] Burger, H. C., and van Milaan, J. B.: Heart vector and leads. Part II. Brit. Heart J. **9:** 154, 1947.

[12] Dolgin, M., Grau, S., and Katz, L. N.: Experimental studies of the validity of the central terminal of Wilson as an indifferent reference point. Am. Heart J. **37:** 868, 1949.

[13] Rappaport, M. B., and Williams, C.: An analysis of the relative accuracies of the Wilson and Goldberger methods for registering unipolar and augmented unipolar electrocardiographic leads. Am. Heart J. **37:** 892, 1949.

[14] Burger, H. C., and van Milaan, J. B.: Heart vector and leads. Part III. Brit. Heart J. **10:** 229, 1948.

[15] Frank, E.: General theory of heart-vector projection. Circulation Research **2:** 1954.

[16] Duschosal, P. W., and Grosgurin, J. R.: The spatial vectorcardiogram obtained by use of a

trihedron and its scalar comparisons. Circulation **5:** 237, 1952.

[17] MILNOR, W. R., TALBOT, S. A., AND NEWMAN, E. V.: A study of the relationship between unipolar leads and spatial vectorcardiograms, using the panoramic vectorcardiograph. Circulation **7:** 545, 1953.

[18] SCHMITT, O. H., LEVINE, R. B., SIMONSON, E., AND DAHL, J.: Electrocardiographic mirror pattern studies. Parts I, II, and III. Am. Heart J. **45:** 416, 1953; **45:** 500, 1953; **45:** 655, 1953.

[19] FRANK, E.: A theoretic analysis of the influence of heart-dipole eccentricity on limb leads, Wilson central-terminal voltage and the frontal-plane vectorcardiogram. Circulation Research **1:** 380, 1953.

[20] —: The zero-potential contour on a homogeneous conducting cylinder. Institute of Radio Engineers Transactions (Medical Electronics) **1:** 27, 1953.

[21] — AND KAY, C. F.: The construction of mean spatial vectors from null contours. Circulation **9:** 555, 1954.

[22] BURGER, H. C., AND VAN MILAAN, J. B.: Heart vector and leads. Brit. Heart J. **8:** 157, 1946.

[23] —, AND DEN BOER, W.: Comparison of different systems of vectorcardiography. Brit. Heart J. **14:** 401, 1952.

[24] LANGNER, P. H., JR., BENJAMIN, J. M., JR., AND MOORE, S. R.: Certain inevitable relationships among the "unipolar" extremity leads. Circulation **5:** 878, 1952.

CLINICAL CONFERENCES

Editor: EDGAR V. ALLEN, M.D.
Associate Editor: RAYMOND D. PRUITT, M.D.

When "Clinical Conferences" were initiated somewhat more than one year ago, the editors solicited contributions from selected authorities. The duplication in the current "Clinical Conferences" is due to lack of alertness on the part of the editors. However, there is virtue in this apparent duplication, because each group of investigators has presented results of study wholly unaware that a similar report would be made by the other group. Readers may benefit more by considering the two publications together than they would have benefited had they read only one report.

The Use of Anticoagulant Drugs in Ambulatory Patients

By EMMET B. BAY, M.D., WRIGHT R. ADAMS, M.D., RICHARD J. JONES, M.D., ROBERT G. PAGE, M.D., AND MORRIS SEIDE, M.D.

SOMEWHAT paradoxically this Conference is emanating from a place where "armchair medicine" is generally frowned upon as a solution to problems. The justification for it rests in the fact that speculation says that the proper use of anticoagulant drugs may well be life-saving to several varieties of patients right now.

The use of anticoagulant drugs has become a more controversial matter in recent years. There has come to be some doubt in the minds of some excellent clinicians about the wisdom of using these preparations routinely in frank cases of acute myocardial infarction. To the experienced cardiologist this is difficult to understand. Here we are not relying on impressions, for our opinion is backed up by the cooperative study of the Committee on Anticogaulant Therapy of the American Heart Association. This group showed that the immediate mortality from acute coronary occlusion was approximately cut in half by anticoagulant treatment. Furthermore, the experienced physician knows that although one can separate "probably good risk" from "probably bad risk" patients with myocardial infarction, it is utterly impossible to pick an individual from among the so-called "good risk" patients who may not have a fatal attack at any moment during his first three weeks of recovery from an acute cardiac accident. These fatalities are brought about by one of several mechanisms. For example, one is the development of ventricular fibrillation, and this obviously cannot be prevented by anticoagulant treatment. However, there are at least three mechanisms of death which are theoretically and demonstrably preventable by these means. One is an extension of the existing thrombus proximally in the coronary tree and a resulting occlusion of an increasing number of branches with a wider and wider area of infarction. A second is the development of a new thrombus at another site in the arteries supplying the heart with blood. A third is the formation of a mural thrombus over the infarcted area on the inside of the heart with subsequent production of embolic accidents of sufficient magnitude to cause death when they happen to hit the brain. We can, therefore, say with great assurance that the treatment of any patient with a fresh coronary thrombosis should include the use of anticoagulant drugs.

It is safer to use heparin alone if one has the slightest doubt about his laboratory control of the doses of other anticoagulants. When adequate facilities are available, anticoagulant drugs which can be given by mouth are to be preferred. It should be stressed that in com-

From the Department of Medicine, University of Chicago, Chicago, Ill.

petent hands there is very little danger in the use of these materials. Even when the patient has a history of bleeding from a peptic ulcer, it is important to protect him in this way when he develops a clot in a branch of a coronary artery. Other entities about which much the same may be said include embolic accidents in the presence of auricular fibrillation or a fresh thrombophlebitis or phlebothrombosis with or without pulmonary emboli.

A more controversial situation with respect to short-term anticoagulant treatment involves the patient with recently developed congestive heart failure. It was shown several years ago at the Mayo Clinic that more pulmonary emboli which complicate congestive heart failure arise from the veins in the legs than from the auricles, and that these are more frequent than is generally supposed. Whether one should use these drugs routinely in the care of patients with congestive heart failure is debatable, and no figures are known to us which settle the point. As the years pass and our experience grows, together with our feeling of security about the use of these admittedly dangerous drugs, we are inclined to use them more freely in this situation.

At the present time, without doubt, there is a very large and honest difference of opinion concerning the indications for the long-term use of anticoagulants in an ambulatory, prophylactic way. The theory, of course, is that by such use recurrences of thromboembolic accidents can be prevented. Figures which will bear statistical analysis supporting this theory are presently unavailable and probably will be for years to come. This is in part because the natural histories of the diseases for which such figures might be used are so variable from person to person, and in part because it will take years to accumulate such figures in any event. The best one can do, therefore, is to speculate and to base one's judgment as objectively as possible on the procedure one would like to have applied to oneself in such a controversial situation. It would seem that in theory these drugs would represent insurance against repetitious trouble. This has to be balanced against the difficulties inherent in their use. To us it has seemed for the past five years, and still does, that the advantages outweigh the disadvantages. We have each had a few patients in whom a succession of thromboembolic accidents was apparently brought to a halt by these means, and we are continuing their use in this way.

We may say that our impressions are based on a review of the histories of 115 patients who had received anticoagulant therapy while they were ambulatory. Their average age was 53.8 years, and there were 84 males and 31 females in the series. They had received treatment by July 1, 1953, for a total of 6,572 weeks, or an average of 57.1 weeks per patient. Sixty-eight patients were placed on long-term anticoagulant therapy because of a recent myocardial infarction and 47 for other reasons. There were hemorrhagic complications in 12 patients, or 10.5 per cent. Of these, six were so minor that the anticoagulants were not discontinued. There were recurrent thromboembolic accidents in four patients, or 3.5 per cent.

We would like, however, to present some of the difficulties we have encountered, rather than emphasize what must remain our impressions of our successes. Perhaps the most frequent problem has to do with the dosage requirement of a few individual patients from time to time. We have one patient, for example, whose Dicumarol dosage has varied during the past four and a half years from as little as five 50 mg. doses of Dicumarol per week to as much as 150 mg. alternating with 100 mg. daily. This, of course, means that the patient has to have a prothrombin time test at least once a week. It may be said in passing that this patient is the most convinced of any of our patients that this treatment is very important to her. She has an old rheumatic mitral stenosis and insufficiency with auricular fibrillation and had had three major arterial emboli in the six months preceding the onset of ambulatory anticoagulant treatment. Two of these involved the extremities and one the brain. Embolec-

tomy was performed soon after the onset of the last of these when she first came here with a cold, pulseless leg. A strikingly similar case, with respect to the clinical picture, is presented by another woman who had essentially the same anatomic diagnoses with respect to her heart and had had three embolic accidents in a period of about one year. Incidentally, she was the only patient we have ever seen where we felt genuine confidence in a diagnosis of embolism in a coronary artery. Her Dicumarol dosage has been among the most constant through four years of any that we have encountered. She is now able to go four weeks between tests and her dosage rarely varies by more than two pills in each four-week interval.

Another patient was placed under treatment with Dicumarol after two episodes of myocardial infarction. (See fig. 1) The figure shows the "prothrombin ratio," which was measured once a week, and the average daily dose of Dicumarol during each week of the ambulatory therapy.* This patient required approximately 50 mg. a day for the first 12 weeks after discharge from the hospital. At the end of this time his prothrombin ratio fell below 33 and reached a low point of 22. The dose of Dicumarol was progressively reduced and eventually was reduced to a level of 14 mg. a day for one week, after which his prothrombin ratio rose and his maintenance dose was approximately stabilized at a level of 40 mg. a day although definite fluctuations persisted. The patient was comfortable during this entire period. He had no angina and no definite symptoms of heart failure. The reason for his episode of sensitivity to Dicumarol was not elucidated. Although he did not

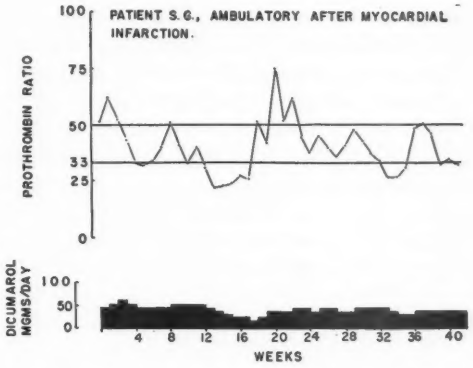


FIG. 1. Response of prothrombin ratio to Dicumarol.

have any hemorrhage or other untoward symptoms while his prothrombin ratio was low, it seems very probable that he would have had trouble had the dose been continued through this phase at a level of 50 mg. a day. This patient provides strong evidence for the necessity of frequent testing of prothrombin time during the administration of this drug.

Many patients seem to be easily controlled under hospital conditions during convalescence from their myocardial infarctions, but the dose established from this experience almost always has to be altered when they resume living at home. One reason for this could be the difference between home and hospital diet, though efforts to evaluate vitamin K intake in the two diets have not been rewarding. Aspirin is well known to have a Dicumarol-like effect on the prothrombin time. One of our patients receiving 4 Gm. of aspirin per day for the treatment of acute rheumatic fever had a prothrombin ratio of 52, though no anticoagulants were being administered. Consequently, our patients are advised to take salicylates sparingly for upper respiratory infections. They are likewise advised to adhere to as constant a diet as possible in the hope that we may at least control this factor. Intercurrent illness itself may affect the prothrombin time, apart from any effect of the diet or medication, but this is unproven. There is little doubt that alcoholic indulgence may

* The prothrombin time ratio as it is used here is the control prothrombin time in seconds times a hundred divided by the patient's prothrombin time. The prothrombin ratio 50 represents a prothrombin time twice the normal control, and the figure 33 three times the normal. These figures are used here as the therapeutic range. It should be noted that there is no rectilinear relation between this prothrombin time ratio and prothrombin activity, nor between either of these and prothrombin concentration or content.

also affect the dosage stability. The explanation for this is not clear, but certainly patients who drink, especially when they drink erratically and excessively, are very difficult to manage on Dicumarol. Antibiotics, too, because of their effect on intestinal flora, may influence dosage requirement.

One other factor which may play a role both in upsetting dosage regulation and creating an additional hazard of hemorrhage is the menstrual cycle. Fortunately, most patients with myocardial infarctions are not menstruating women. However, one female patient, aged 56, suffered a myocardial infarction and was started on Dicumarol therapy some six months after her last menstrual period. She also had had hot flashes and a few other minor symptoms of the menopause. On starting Dicumarol she had a resumption of the menses which was both erratic and excessive in its extent, even though her prothrombin levels were within what we consider the therapeutic range. Dicumarol finally was discontinued after three episodes of vaginal bleeding, the final one lasting for a period of two weeks. She had no more menstrual bleeding in the subsequent two years.

A younger woman, aged 41, was placed on anticoagulants because of embolic phenomena consequent to auricular fibrillation and congestive heart failure. She seemed to have a tendency to go below the therapeutic range late in each menstrual cycle so that on three successive occasions her menstrual period came at a time when the hemorrhagic tendency was most marked. Her hemoglobin fell to 9 Gm. per 100 cc. and had to be restored by transfusion on the last occasion. It was impossible to be certain whether the menstrual cycle was responsible for this woman's cyclic prolongation of the prothrombin time or whether it was simply due to the vagaries of Dicumarol administration, but it was deemed inadvisable to continue the medication. This same sort of cyclic variation seems to be present in another menstruating patient now on Dicumarol therapy for thrombophlebitis. However, her fluctuation does not seem to be as great and may yet permit successful control of prothrombin time without hemorrhage. In any event we feel that the use of anticoagulants in ambulatory menstruating women can be very hazardous and requires close observation; it may in some cases be virtually impossible.

We have encountered the rare patient, usually during the treatment of an acute situation, but sometimes during chronic care, in whom overdosage of Dicumarol has led to a prolongation of the prothrombin time beyond the three times normal which we regard as the therapeutic level for as long as seven or eight days after the drug was stopped. In none of these patients has any demonstrable bleeding occurred during the protracted period of hypoprothrombinemia.

As was indicated earlier, the problem of accurate laboratory control of Dicumarol dosage has been a major concern of all of us from the very beginning. Determination of the prothrombin time, no matter what method is used, seems relatively simple in theory and surprisingly difficult in practice. Among other things, we have learned that it is important to have the same person draw all the bloods so that he will know of the possibility of a vitiated test because of a difficult venepuncture. We have learned that we have to sharpen our own needles to guard against excessive tissue damage at the time of the withdrawal of blood. We have tried to make the test more objective by various means, the latest being the use of a recording milliammeter and a motor-driven tilting tube. This last gives some promise of being useful but is not yet in the stage where we wish to recommend it to others.

A factor in the test which has only recently come to light is the effect of severe emotional stress upon the prothrombin time. This is well illustrated by one of our patients who has been on ambulatory Dicumarol therapy for about four years. His dosage stability was such that he usually required a test every two weeks to keep him within the therapeutic range. Since he lives 180 miles from Chicago, we made an effort to find a laboratory nearer his home which could perform the test accurately. For the first five times the test was performed near his home, and, three hours later, in Chicago with strikingly good duplication of results. Thereafter he was double-checked only once every three months, always with satisfactory comparsions

until the occasion about to be described. This time he had the test made near his home about 8 a.m. and then drove to Chicago. It was during the month of January; the weather forecast had been faulty, and the hazardous driving conditions that obtained had not been predicted. On entering the city limits on a major bouelvard, with his wife driving, the car went into an alarming skid but, miraculously, did not collide with any parked cars nor with oncoming traffic. However, being in the automobile business, the patient was all too well aware of what might have happened and was, as he later said, as "scared as he ever had been in his life." He was still weak and trembling when he had his prothrombin test in Chicago. For the first time there was a sharp disagreement between values found by the two laboratories. Subsequent checks were again in accord. While this is an extreme example of the effect of fear upon the results of the prothrombin time test, it is quite possible that, in those patients who dread needles, similar, though less dramatic, effects might be encountered.

We have seen a fairly large number of very minor hemorrhagic tendencies in ambulatory patients on long-continued Dicumarol therapy. Most frequently these have been small ecchymoses of the skin or microscopic blood in the urine or epistaxis. A few have had bleeding gums. Of slightly greater moment was a hematoma of the soft palate. We have had six instances of more massive hemorrhage. Three of these have been from the gastrointestinal tract, one consisted of gross hematuria, one was a hemorrhage into a joint, and one resulted in a large hematoma of the thigh. All were quickly brought under control by whole blood transfusions and large doses of vitamin K. The case of greatest interest in this category was one in which there was a known history of bleeding peptic ulcer on two occasions before the patient had his first myocardial infarct. He was treated with anticoagulant therapy during the acute phase with no untoward results. He was not placed on anticoagulant treatment in an ambulatory fashion because of the history of massive gastric hemorrhages. He had a second coronary thrombosis about four months after the first one and again received anticoagulant therapy successfully during the acute phase. The question of the use of anticoagulants over a long period of time in the presence of a history of bleeding ulcer was a difficult one. The problem was explained to the patient, and it was suggested that he take a calculated risk and try them. He took Dicumarol with surprisingly little variation in his maintenance requirements for over a year when he had his third massive gastric hemorrhage. His prothrombin time was just slightly over twice the laboratory's control value for that day at the time the hemorrhage occurred. The hemorrhage was readily treated with whole blood transfusions and he was advised not to attempt to continue on ambulatory anticoagulant treatment. However, he remembered the intense pain of his two episodes of coronary thrombosis so vividly and he had so little fear of gastric bleeding since he had had it three times with no prolonged convalescence, thanks to the use of multiple transfusions, that he insisted on taking Dicumarol again and stated that he would find some doctor who would give it to him if we would not. Our own impressions of the efficacy of this form of preventive treatment were so encouraging and by this time our dread of hemorrhagic complications was so allayed, that we acquiesced. He has been on anticoagulants ever since with no thrombotic complications nor any hemorrhagic ones.

An interesting patient illustrated the fact that Dicumarol may be extremely valuable in situations where its use seems very dangerous. He was 46 years old when we first saw him in 1944. At that time he gave a history of having had rheumatic fever at the ages of 13 and 19 years, which had caused him no trouble until the age of 45 when symptoms of heart failure began. He also gave a history of having had a peptic ulcer which began at the age of 30 but had caused no symptoms for the five years preceding our contact with the patient. He was successfully treated for heart failure from 1944 until 1946 when his ulcer again became active. Although partially disabled, he did rather well until 1949 when he had the first of a series of acute illnesses which were at first thought to be severe upper respiratory infections. Between 1949 and March of 1951 he had seven severe

recurrences of a febrile illness accompanied by cough and diffuse radiographic density in the lungs. He had several minor episodes which were not recorded. In March of 1951 a particularly severe episode was accompanied by hemoptysis and a localized density in the lung which was typical of pulmonary embolism. This possibility had been considered on several previous occasions, but a satisfactory diagnosis had not been established. In March of 1951, because it was concluded that most, if not all, of these episodes had in fact been pulmonary embolism, he was placed on Dicumarol and maintained on it until January of 1953. During this time he had no recurrences of the acute febrile episodes associated with respiratory symptoms. On Jan. 8, 1953 he suffered a massive hemorrhage from the stomach originating in his gastric ulcer. He was brought into the hospital, treated for the hemorrhage and the anticoagulants stopped. The prothrombin ratio returned rapidly to normal as a result of several transfusions. His stools had become negative for blood by the end of the month. On February 15 he developed a pulmonary embolism with an acute febrile illness similar to those which he had had before anticoagulant therapy was introduced. Because of the obvious danger to the patient's life, Dicumarol was started again and the prothrombin ratio maintained within therapeutic range. After it had been in therapeutic range for a week the stools again became positive for blood although there was no gross hemorrhage. At this time he began to complain of severe epigastric pain. Anticoagulant medication was continued and in spite of this the stools became negative for blood on February 26. They remained negative until March 1 when, because of the intractable ulcer disease, he committed suicide. It is almost certain that this patient's life was prolonged by the use of anticoagulants although they were dangerous because of the ulcer and there were two episodes of hemorrhage, one of which was severe.

In one of the patients who had massive gastrointestinal hemorrhages no lesion could be demonstrated in the gastrointestinal tract by any of the usual techniques of examination. The patient who had gross hematuria was known to have had bilateral renal calculi for many years. He suffered a coronary thrombosis which was an extensive one in that he had mild, but real, objective evidence of some congestive heart failure. Even though he was on anticoagulant treatment and was within the therapeutic range of prothrombin time determinations, he suffered an embolic accident to the right leg about two and a half weeks after the onset of his coronary thrombosis. He had had microscopic hematuria for years but did not show any increase in this during his anticoagulant treatment for the acute phase of his illness. Again the difficult decision had to be made as to whether to advise the use of Dicumarol in an ambulatory fashion. It was felt that his cardiac reserve was so seriously reduced that if there was any hope of preventing a recurrence of myocardial infarction it was worth the risk. He was continued, therefore, on anticoagulant treatment successfully for about seven months when he had a gross hematuria for the first time. However, this was readily treated successfully, and the fact that his hemoglobin and red blood cell count were hardly altered by this episode suggests that he did not lose very much blood. However, the drug was stopped. He died a few weeks later at home, the cause of death being uncertain since he was found dead in the morning. The presumption was high, however, that he had another thrombotic episode involving either the coronary or the cerebral vessels. Of course, he could have had ventricular fibrillation, but this is not so likely as either of the other two entities.

An example of an embolic accident occurring during Dicumarol administration was the case of a 66 year old man who was hospitalized in September 1951 for an acute myocardial infarction and started on Dicumarol therapy. He was maintained with "ambulatory Dicumarol" after the initial convalescence with some difficulty, presumably because of his drinking habits. On Oct. 25, 1952, approximately one year after his myocardial infarction, he was readmitted with a history of pleuritic type of right-chest pain which had developed suddenly 12 hours previously. Although there was no hemoptysis or cough, there was some dyspnea and fluoroscopy revealed a wedge-shaped shadow in the right anterior lobe of the lung where a

friction rub could be heard. The morning after this occurrence his prothrombin activity was still within the therapeutic range (46 per cent) where it had been for some weeks. There was no evidence of congestive heart failure, recurrent myocardial infarction, or any of the usual acute factors predisposing to intravascular thrombosis.

Some stubborn questions remain which have no easy answers: When should patients on long-term anticoagulant therapy discontinue their medication? Should patients with auricular fibrillation and embolic accidents ever have Dicumarol discontinued? How long after an acute myocardial infarction dare we stop ambulatory anticoagulant therapy, if it is to be stopped at all? Embolic accidents usually occur in patients with auricular fibrillation, either when the fibrillation is uncontrolled by digitalis or when there are other manifestations of congestive heart failure. Consequently, some of us have been willing to discontinue Dicumarol in such patients when both failure and auricular fibrillation were unequivocally controlled for periods of several months. Some evidence has been introduced to indicate that the likelihood of recurrence of a myocardial infarction falls considerably after the first two or three years, and it has been suggested that the life expectancy of a patient who is still ambulatory two or three years after a myocardial infarction approaches that of the rest of the population of the same age and sex. This gives us a logical basis for stopping anticoagulants in anyone who is ambulatory and essentially asymptomatic, except perhaps for occasional bouts of angina pectoris, sometime between two or three years after the initial episode. Because of the hazard which cold weather brings to these people, it would seem preferable to discontinue the drug in the late spring. This, of course, is still an arbitrary pattern based on slender evidence which is an effort to compromise with those who would continue ambulatory anticoagulant therapy indefinitely and those who never use this form of treatment. There is a difference of opinion among the authors on this point but complete agreement on the wisdom of using these drugs in selected ambulatory patients for varying lengths of time.

Long-Term Anticoagulant Therapy

Participants: Irving S. Wright, M.D., Chairman, Rene-Henri Bourgain, M.D., William T. Foley, M.D., Ellen McDevitt, M.D., Clara Gross, M.D., Grafton Burke, M.D., Eugene Simon, M.D., Jerrold Lieberman, M.D., Cecil Symons, M.D., and Robert Huebner, M.D.

DR. IRVING WRIGHT: The subject for the conference today is long-term anticoagulant therapy.

The possibility of long-term prophylactic and therapeutic anticoagulant therapy was a natural sequence to its successful use for acute thromboembolic conditions. It did necessitate a marked revision in both the technical and the philosophical approach to such conditions as recurrent thrombophlebitis, myocardial infarction, auricular fibrillation which was responsible for multiple emboli, and numerous other thromboembolic conditions. From a static and resigned approach in which the patient and physician alike awaited with apprehension the possibility of a series of serious or even fatal developments, it was conceivable that a dynamic attack might be at least considered, with physiologic and psychologic advantages to the patient.

In 1946 we reported our preliminary experience with Dicumarol for long-term management of patients with rheumatic heart disease with auricular fibrillation and multiple emboli. It is of interest that of the small number of patients then reported on, several of them are still alive and in reasonably good health. An outstanding example is a woman who had suffered a total of 21 recognized emboli prior to her anticoagulant therapy. She had nine emboli of sufficient significance to be recognized clinically; some of the resulting episodes were serious in the 10 days before anticoagulant therapy was inaugurated. She is still alive and active. She was placed on anticoagulant therapy on Nov. 6, 1946. The only embolus that has been recognized from that date until the present was one which occurred in June of 1950, after 30 days without anticoagulant therapy. About June 1, 1950 she decided that she was probably safe from the danger of emboli although she was still fibrillating. She was bored and tired of prothrombin tests at weekly intervals and discontinued the therapy. Just 30 days later she had a saddle embolus. Fortunately, this disintegrated. The fragments descended into the small vessels and serious consequences were averted. She then decided to resume therapy and has suffered no further emboli.

Subsequently, Nichol and Fassett[1] have reported experiences with long-term therapy in an attempt to forestall acute myocardial infarction and we have published additional observations on larger groups of cases. Also Sprague and Jacobson[2] of Boston, Cosgriff[3] of New York and Askey and Cherry[4] of Los Angeles have reported experience with this form of therapy. While the data regarding such long-term therapy are difficult to evaluate because of the countless variables that are introduced by the active lives of individuals, those who have watched these cases have been impressed with the probability that the course of these patients has usually been favorably affected. It has been clearly demonstrated, furthermore, that long-term therapy is practical. It is entirely feasible with certain provisions, and patients on long-term anticoagulant therapy can in many instances be self-supporting and productive citizens.

After our experience had multiplied with the passage of years, Dr. Tulloch summarized our observations on 227 patients cared for in private practice or in the Ambulatory Clinic at the New York Hospital.[5] This study represented a total of 180 years and 124 days of anticoagulant therapy. One hundred and

From the Cornell University Medical College, New York, N. Y.

Based on a peripheral vascular disease conference held on Wednesday, Oct. 14, 1953.

Eighty-two patients received Dicumarol for 59,104 days and 53 patients received Tromexan for 6,700 days. This experience is sufficient to be of some interest. Since Tulloch compiled these data we have increased our experience so that the total now approximates 300 such patients. A report dealing with this experience has been accepted for publication by this journal.

There are certain indications for long-term anticoagulant therapy, but each case must be subject to the decision of the physician.

Indications

I. Multiple embolization in patients with rheumatic heart disease and auricular fibrillation.

II. Recurrent thrombophlebitis, especially if the recurrences occur at very short intervals of time.

III. Multiple arterial occlusions, if it is believed that thrombosis or embolism is playing the causative role.

IV. Recurrent myocardial infarction, especially if thromboembolic complications are evident.

V. Idiopathic or familial thrombosing conditions.

VI. Idiopathic and recurrent pulmonary embolism or thrombosis in which the original site of thrombus may never be known.

VII. Less well-defined indications include recurrent angina pectoris, which suggests impending coronary occlusion. This applies to the person who is unable to be active without suffering anginal pain which is becoming sufficiently frequent and severe to convince the physician that there is danger of a coronary thrombosis. Another less well-defined indication is with recurrent evidence of cerebral vascular spasm or multiple small thromboses.

Technic

The technic we have used is somewhat as follows: The patient is preferably admitted to the hospital where an endeavor is made to standardize his dosage requirements, whether he uses Dicumarol, Tromexan, Cyclocumarol, Hedulin, or any of the new anticoagulants. After 7 to 10 days he can usually be controlled by the use of prothrombin-time tests taken once a week. Occasionally a patient requires a test twice a week if his prothrombin time tends to fluctuate very much. With Dicumarol the dosage has been from 25 mg. to 125 mg. a day. It is impossible to predict how much a patient will require for proper control. The dosage requirement will vary from time to time, but over a period of several years the average for a specific patient will remain fairly constant in most instances. The desirable levels of prothrombin time for patients on long-term therapy are between 23 and 33 seconds (50 to 25 per cent prothrombin activity) because a person who is ambulatory is more subject to trauma and dietary disturbances, which may affect anticoagulant utilization, than the patient who is under complete hospital control.

Contraindications

It should not be forgotten that there are certain contraindications, or indications for the cautious use of these substances. They include: (1) hypoprothrombinemia due to vitamin K deficiency or severe hepatic disease; (2) vitamin C deficiency (until this is remedied); (3) renal insufficiency of a marked degree; (4) blood dyscrasias with bleeding tendencies; (5) surgical and other trauma which leave large, open, raw surfaces, exposure of the brain or spinal cord and operations in the presence of obstructive jaundice or severe liver disease; (6) ulcerations or cancer of the gastrointestinal tract, the genitourinary tract, or other sites at which bleeding may be easily induced; (7) subacute bacterial endocarditis, although as Dr. Huebner pointed out recently,

TABLE 1.—*The Equivalent Values of Time to Percentage of Prothrombin Activity as Used in This Study*

Seconds	Per cent
15–16	100 (Normal-Control)
23–27	50
30–33	25
36–41	12.5
60+	10–0

Optimal therapeutic range for long-term anticoagulant therapy is considered to be between 23 and 33 seconds or approximately 50 to 25 per cent of prothrombin activity.

this subject has not been fully re-evaluated in recent years.

These are general contraindications for either acute or chronic anticoagulant therapy. There are additional contraindications which pertain to long-term therapy: (1) Marked hypertension. A level above 200/110 is an indication for great caution if the drug is used at all. Even lower levels of pressure may be equally important if there has been any evidence of vascular damage. (2) An irresponsible or mentally incompetent patient. Once the patient leaves the hospital the physician no longer has control over whether he does take the drug when he is expected to, whether he comes for his tests of prothrombin time when he is supposed to, or other factors which may enter into the picture such as alcoholic bouts and deprivation of proper food, and so forth. (3) A physician who is not well trained in this work or who does not wish to assume the responsibility for this rather demanding and meticulous form of therapy.

It may be said that while there appears to have been a marked diminution in the number of thromboembolic complications in our patients on long-term therapy, thromboembolic episodes have occurred at all levels of prothrombin time. They have occurred at levels below 20 seconds; they have occurred at levels between 20 and 24 seconds; they have occurred between 24 and 40 seconds; and they have even occurred at prothrombin times above 40 seconds. This is evidence that there is great complexity and variation in the mechanism concerned in thromboembolic tendencies, and, whereas with these drugs we may take care of the prothrombin and perhaps factor VII and V, there are still other aspects of the clotting mechanism which may outweigh these factors from time to time in a given patient. Actually, while on anticoagulants only 26 patients of our rather large series had a total of 40 clear or doubtful thromboembolic complications; of the latter 16 were very doubtful.

Hemorrhages also occurred at all prothrombin levels. Bleeding should not always be attributed to anticoagulants simply because a patient happens to be taking them at the time. Control groups of patients not on anticoagulants also have hemorrhages, although this fact is often overlooked With pulmonary emboli they have hemorrhages from the lung; with renal emboli they have urinary bleeding; with emboli to the wall of the gut they may have a hemorrhage from their bowels. In other words, all hemorrhages which occurred in this series were not necessarily due to anticoagulant therapy, but we have so listed them nevertheless. The majority of these hemorrhages occurred at prothombin levels over 25 seconds, and there is a much higher incidence above 40 seconds. There has been one death in this series which we believe to have been due to anticoagulant therapy. This was a cerebral hemorrhage in a patient with hypertension, but since the indications for anticoagulant therapy were very strong, a calculated risk was assumed. In the event of major hemorrhage the patient was given either one or two transfusions of 250 to 500 cc. of whole fresh blood or 250 mg. to 500 mg. of vitamin K_1. For minor bleeding, discontinuance of the anticoagulant and the administration of 70 to 150 mg. of water soluble vitamin K was usually sufficient.

These patients on long-term anticoagulant therapy have survived accidents and surgery successfully. Before a surgical procedure is undertaken, it is advisable to reduce the dosage of the anticoagulant for a day or two, or by other means bring the prothrombin time down to a normal or nearly normal level. Surgery is not contraindicated during the type of treatment we are discussing provided that the proper steps are taken to prepare the patient; the prothrombin time should be normal.

The first case to be presented this afternoon is a case of recurrent myocardial infarction which will be presented by Dr. Rene Bourgain.

DR. RENE BOURGAIN: Mr. A. J., an orderly in this hospital, is a 47 year old white man. His past history is not significant. His father suffered from diabetes.

The patient was symptom-free until December, 1944, when, after seven days of substernal discomfort, he suddenly experienced a severe stabbing pain in the same area. There was no previous history of angina. He was admitted to this hospital, the electrocardio-

gram revealing an acute anterior myocardial infarction. The white blood cell count was 24,000 and the blood pressure 145/90. The patient did not complain of further pain and he made an uninterrupted recovery. He was discharged in February, 1945, without any signs of cardiac failure. His blood pressure was 120/80. He was followed in the Cardiac Clinic and received aminophylline and nitroglycerine. An electrocardiogram taken later showed that T_1 had become positive. He was free of symptoms until August, 1949, when he suffered two anginal episodes, each of about five minutes duration. An electrocardiogram taken at this clinic showed minor posterior-wall changes and a second electrocardiogram taken about three days later revealed a definite pattern of acute infarction of the posterior wall of the left ventricle, and he was therefore readmitted. On physical examination at this time he had rales at the base of the left lung, and the blood pressure was 120/70. Two weeks after his admission, and after consultation with the vascular clinic team, it was decided that the patient should receive anticoagulant treatment, and he was started on Dicumarol. This was continued for nearly a month and the maximum prothrombin time noted was 42 seconds.

He was free of symptoms for about 18 months and an electrocardiogram made in December, 1950, revealed no signs of further myocardial infarction, T_1, T_2 and T_3 being upright. In January, 1952, he again complained of severe localized left anterior chest pain accompanied by severe dyspnea. He was admitted for the third time. His blood pressure was 130/70 and there were rales at both lung bases. The electrocardiogram was characteristic of anterior wall infarction. There was a small Q_1 and deep Q in V_5 with negative waves in leads I, V_5 and V_6. After about three days his pain subsided. He was again placed on anticoagulant therapy for one month. During hospitalization he developed a perianal abscess which subsided without complications. He was discharged on Feb. 7, 1952, with a blood pressure of 120/70.

After discharge he was free of symptoms again, but only for six days, when he was admitted for the fourth occasion with severe pain and a negative T_1 in the electrocardiogram. It was then decided to institute long-term anticoagulant treatment with Dicumarol. The maximum prothrombin time during hospitalization was 45 seconds. He was discharged in February, 1952, and has been continuously on anticoagulant treatment except for five days during August, 1952, when he was again admitted with a chill, fever and diarrhea with bloody stools. Diagnoses of *Salmonella enteritis* and pneumonia were among those considered. Stools were negative on culture and the only positive finding was a bilateral maxillary sinusitis on radiologic examination. Anticoagulant treatment was started again five days after admission and has been continued to date.

The patient was discharged in August, 1952, his prothrombin time being 27 seconds. On four occasions since long-term therapy was started his prothrombin time has reached 45 seconds or more. He was admitted for surgical drainage of his perianal abscess in August, 1953. The patient's general condition is good, but he has developed an anxiety state. He occasionally has anterior chest pain, but not typically anginal in character.

To summarize, we have presented a patient who has had four recognized episodes of acute myocardial infarction and has been under long-term anticoagulant therapy since 1952 without any further thromboembolic complications.

(*Patient comes in.*)

DR. WRIGHT: How are you feeling?

PATIENT: Very well.

DR. WRIGHT: Do you have any pain?

PATIENT: Not now, sir.

DR. WRIGHT: We have nothing particular to demonstrate. You have had four attacks?

PATIENT: Yes, sir.

DR. WRIGHT: When was the last one?

PATIENT: January '52.

DR. WRIGHT: You work as an orderly?

PATIENT: Yes, sir.

DR. WRIGHT: You are able to shift patients about?

PATIENT: I do the best I can, sir.

DR. WRIGHT: Are there other questions anyone would like to ask Mr. J.? (*Patient leaves.*) Dr. Foley, do you have some comments about this problem of the use of anticoagulants

in the treatment and prevention of recurrent myocardial infarction?

DR. WILLIAM T. FOLEY: This problem presents a challenge to the medical profession and there had been no previous treatment offered that could possibly prevent recurrence of coronary artery thrombosis. With this in view Dr. Wright and I initiated long-term anticoagulant therapy in a series of patients. A preliminary report appeared in February, 1948. Of the original five patients who were placed on this form of therapy because of recurrent myocardial infarction, four are still living after a minimum of six years. Since that time we have maintained an additional 10 patients, bringing the total number to 15, all of whom have been on anticoagulant therapy for a period now which averages five years for each person. In this entire group there have been three deaths. One of the group had to abandon therapy because of bleeding in the urinary tract, and genitourinary investigation disclosed a congenital abnormality of the kidney. One of the patients abondoned treatment because of difficulty in having his prothrombin time tested. One month after abandoning therapy he died, apparently of coronary thrombosis. There have been no major problems with the rest of the group. There have been minor incidences of hemorrhage but no hemorrhage requiring hospitalization or requiring more than temporary withdrawal of the drug.

DR. WRIGHT: Are there other questions?

DR. BOURGAIN: We all know that some cardiovascular conditions, especially coronary disease, are accompanied by hypercoagulability of the blood. At the time that the patient, Mr. J., complained of a severe pain in the chest, the electrocardiogram showed posterior wall changes. Although not unequivocally diagnostic of infarction, this electrocardiogram showed alterations not present in the previous electrocardiogram. I believe that at that time treatment by heparin was indicated. Do you agree?

DR. WRIGHT: That brings us to a very important point in this discussion. If a person develops an acute thromboembolic episode of whatever nature, and you wish to obtain the maximum effectiveness in the shortest period of time, heparin should be used to initiate therapy. That is the great advantage of heparin. It cannot be continued effectively over a period of years. I believe, with Dr. Bourgain, there was a definite indication for heparinization at the time of the premonitory symptoms in this case. It is, however, difficult to know with certainty whether the course of the individual patient has been altered by this approach.

In a specific case one may question whether the patient has had an actual thrombosis. The more than 90 cases autopsied and studied very carefully for the Committee on Anticoagulants of the American Heart Association indicated that more than 70 per cent of all myocardial infarctions resulted from coronary thrombosis.[6]

Frequently the indications are more clear-cut than they are with the patient we are discussing. We have followed a patient who had four very severe myocardial infarcts within a period of six months, following which he was placed on long-term anticoagulant therapy. He has never had a recurrence of myocardial infarction. He leads an extremely active life as both the president and chairman of the board of one of the nation's largest corporations. He flies in company planes from one part of the country to another visiting plants, but he continues his anticoagulant therapy. He has physicians in most of the cities that he visits who are well trained in the field, and he goes once a week to have a prothrombin time taken; he can now adjust his life and his anticoagulant therapy accordingly. I mention this patient to indicate the feasibility of an active life on such a regimen.

The next patient has suffered from recurrent thrombophlebitis with pulmonary emboli. Dr. McDevitt will present this patient.

DR. MCDEVITT: Mr. V. J. is a 50 year old postal clerk who was essentially well except for bronchial asthma which recurred yearly. In 1947, at the age of 44, three months after a right herniorraphy, he developed a right saphenous thrombophlebitis which necessitated six weeks' rest in bed. Following ambulation he wore an elastic stocking. In 1948 he had a

recurrence of thrombophlebitis in the same leg, and in 1949 he had two episodes of thrombophlebitis involving the same extremity. This patient was first seen in the New York Hospital in March 1950. Three weeks following the onset of pain, swelling and redness in the right extremity, and one week prior to admission, he experienced a sudden onset of sharp pain in the right chest, and one day prior to admission he had hemoptysis. On admission his vital signs were within normal limits. The temperature was 37.4 C., respirations 20, pulse 80, blood pressure 135/80. The positive findings included diminished breath sounds at the base of the right lung and a swollen, red, tender right lower extremity. He was started immediately on heparin and Tromexan; he made a fairly satisfactory recovery and was discharged but was not maintained on anticoagulants.

Twenty-three days after his discharge, on May 2, he was readmitted to this hosptial because of recurrence of the thrombophlebitis in the right leg. At this time there was no chest pain. He was restarted on anticoagulants, and it was decided at that time to maintain him on long-term anticoagulant therapy. He was followed in the Anticoagulant Clinic until September 18 of that year, approximately three months later, when he developed an episode of rectal bleeding which was thought to originate in external hemorrhoids. He was seen in the emergency clinic, in this hospital, and the anticoagulant therapy was discontinued. The prothrombin time was 37 seconds. Approximately three days after the anticoagulant was discontinued he experienced sudden, sharp pain in the left chest associated with hematemesis. He was readmitted to the hospital. On this occasion he was febrile for two weeks, and on one occasion his prothrombin time reached 91 seconds following an accidental overdosage of Dicumarol. This prothrombin time was quickly brought under control by using 72 mg. of water soluble vitamin K. He was discharged on Nov. 1, 1950, and he has been maintained since that date on Dicumarol. His average dose is 50 mg. a day and his prothrombin times have ranged between 24 seconds and 41 seconds. On three occasions when he has been out of town for three weeks his times have dropped to around 19 seconds, but they have very quickly been restored to their average level, and he has had no recurrence of the thrombophlebitis. You will note that he had seven episodes of thrombophlebitis prior to the institution of long-term treatment.

DR. WRIGHT: Bring the patient in. (*Patient comes in.*) Have you had any trouble lately?

PATIENT: None with my legs since 1950.

DR. WRIGHT: Do your legs swell at night?

PATIENT: No.

DR. WRIGHT: No pains or tenderness? Do you have any pains when it rains?

PATIENT: No.

DR. WRIGHT: A great many people after severe thrombophlebitis do have pains with changes in the barometric pressure. I call them weather "veins," a rather poor pun but not without point.

PATIENT: It does not seem to affect me that way.

DR. CLARA GROSS: Do you wear elastic stockings?

PATIENT: Yes.

DR. WRIGHT: On both legs?

PATIENT: Only the right leg.

DR. WRIGHT: Are there any other questions? Thank you very much for coming. (*Patient leaves.*)

This has been a very difficult syndrome in the past because there seemed to be no way of preventing these individuals from having recurrent thrombophlebitis. Some individuals have had 40 or 50 attacks over a period of many years. Each attack has incapacitated them temporarily to a marked degree and left its long-term scar in an accumulative diminution of the active venous system. As a result they develop chronic edema, ulcerations of the ankle, various types of eczematoid reactions and other painful disabling lesions. It was found that if the thrombus occurred peripherally in the saphenous system, ligation might prevent pulmonary emboli, but ligation does not prevent recurrent attacks of thrombophlebitis.

We have studied for six years a retired army colonel who first had saphenous ligation, then

a femoral ligation, and finally an inferior vena cava ligation. He still continued to have recurrent thrombophlebitis of the veins of his legs and pulmonary emboli. Anticoagulant therapy controlled his situation.

We have recently had another patient in the hospital who has had recurrent pulmonary emboli following an inferior vena cava ligation performed after many episodes of thrombophlebitis. In other words, if there is a thrombosing tendency in the blood, it is not necessarily confined to the vessels of the lower extremities, although they are the most frequently involved. So it seems physiologically and pharmacologically sound to attempt to weigh the balance of the thrombosing mechanism against ease of anticoagulation, and yet try not to produce a hemorrhagic state. This we can now do with anticoagulants. Many such patients have now been followed for periods of years. It is of note that even after several years, if prothrombin times are allowed to return to normal, thrombophlebitis may become active again. In certain patients thrombophlebitis will develop if the prothrombin time shortens to under 23 or 24 seconds. At levels of 30 seconds or higher, they are safe from this risk. We do not understand why their blood has this thrombosing tendency. Even rather detailed surveys of many of the clotting factors may fail to reveal any significant alterations from the normal. This merely emphasizes the limitations of our technics.

Dr. Foley: This patient presents one of the key problems in ambulatory anticoagulant therapy, namely, at what level to maintain the prothrombin time. When his prothrombin time was only 33 seconds, he had rectal bleeding. When it was shortened to below 25 seconds, he again developed thrombophlebitis. There are a few patients who must be maintained within a very narrow range. These represent a real challenge to the clinician, but they are usually in serious danger if untreated, so the calculated risk must be taken.

Dr. Burke: Drs. Overman and Link[7] were able to protect rats better from hemorrhage by having them on small doses of vitamin C. Should our patients on long-term therapy, even though they have no evidence of a scorbutic state, receive supplementary vitamin C?

Dr. Wright: That might be taking every precaution, although where there is no evidence of vitamin C deficiency its supplementary administration might not have a very valid scientific basis. It is reasonable and safe to give any patient with any abnormal bleeding tendency rather large doses of vitamin C, such as 600 mg. of ascorbic acid a day, which frequently exceeds their requirements but is harmless.

Dr. Gross: Following a single episode of thrombophlebitis, how long would you continue anticoagulants?

Dr. Wright: Usually until all evidence of thrombophlebitis, such as redness, heat, tenderness and local swelling (except perhaps a remnant of a hard cord which may remain for many months) has subsided, until the pulse rate has returned to normal, and until the sedimentation rate is normal. This usually takes from 10 days to three weeks. For rather severe bouts of thrombophlebitis we may continue anticoagulants for an extra week or so after the patients are up and about and even after they leave the hospital. For recurrent thrombophlebitis, long-term anticoagulant therapy must be considered.

A Physician: Is there any valid evidence that when anticoagulant therapy has been stopped, the patient has a greater risk of a recurrence of thrombophlebitis than a patient who has never been on it?

Dr. Wright: This hinges on the question whether there is an overswing when the blood prothrombin level approaches normal. I think the evidence on this is rather meager. There are patients who have been on anticoagulants for a long time who had thrombi or emboli after anticoagulants were stopped, but usually this occurred from two weeks to two months later. That seems a long time for an overswing to be effective. We have never been able to measure the overswing from coumarin compounds satisfactorily. With heparin a temporary overswing seems a little more likely. More probably this is a manifestation of the former tendency to thrombosis which has now

been released by the elimination of the anticoagulant therapy.

There are many drugs and other factors which affect the dosages of anticoagulants of the coumarin type. For example, if the patient on anticoagulant therapy receives gut-sterilizing antibiotic therapy (Aureomycin, for example) the dosage of Dicumarol or Tromexan may have to be substantially reduced. The theory for this phenomenon is not established beyond doubt, but it is quite likely that the sterilization of the gut interferes with the production of vitamin K, which ordinarily may act as a buffer substance against the coumarins.

We will now consider the last patient, a woman with rheumatic heart disease with auricular fibrillation and recurrent emboli. This is to be presented by Dr. Eugene Simon.

DR. EUGENE SIMON: The patient, Mrs. B. J., is a 43 year old housewife. Her history of rheumatic disease began at the age of six years when she had an episode of chorea. At the age of 13 the patient learned of a heart murmur. She first developed signs and symptoms of heart failure at the age of 21, during her first pregnancy. She was first seen in the New York Hospital Cardiac Clinic at the age of 28. At that time the diagnosis was rheumatic heart disease with mitral stenosis, mitral insufficiency and aortic insufficiency. There was a normal sinus rhythm. Slight cardiac enlargement was noted.

The patient was treated at the age of 31 for an episode of acute rheumatic fever. Between the ages of 33 and 38 she was seen regularly at New York Hospital and she was continued on digitalis because of persistent symptoms of heart failure. During this period normal sinus rhythm was consistently reported. Between the ages of 38 and 41 the patient was not seen at New York Hospital.

Late in 1951, when the patient was 41 years old, she reappeared, complaining of left hemiparesis and left hemihypesthesia with severe headache. At this time for the first time auricular fibrillation was noted. The neurologic diagnosis was considered to be cerebral embolus. The patient was treated with Dicumarol and the symptoms of paresis and hypesthesia subsided fairly promptly. The Dicumarol was discontinued after a few weeks. About seven months later she complained of sudden onset of severe right costovertebral angle pain. This pain was similar to that which one might expect in renai colic and was accompanied by hematuria. Urologic studies revealed no function in the right kidney, and there was a great deal of doubt about the actual diagnosis in her case. Because of the presence of rheumatic heart disease with auricular fibrillation and because of the evident inability to visualize any obstructions in the right kidney, the most likely diagnosis was considered to be embolus to the right kidney. The patient was therefore restarted on anticoagulants. There was a gradual reappearance of function in the right kidney, and it seemed fairly certain at the time of her discharge that she actually had had a large renal embolus. It was felt that this was an appropriate case for long-term anticoagulant therapy because of her having had two serious episodes of embolization in the course of one year and because of the persistence of the factors that seemed to be conducive to her thromboembolic tendency, namely, the mitral heart disease, and rheumatic heart disease and auricular fibrillation. Since the time of her 1952 admission, somewhat more than one year ago she has been maintained on Dicumarol. During this past year she has taken approximately 50 mg. of Dicumarol per day. Her prothrombin times have been determined at either one- or two-week intervals and they have usually been between 25 and 35 seconds. There have been no other complaints or symptoms to suggest any other embolic phenomena. There have been no hemorrhages. In addition to Dicumarol she is receiving digitoxin and Thiomerin. She is able to perform her duties as a housewife and at times has engaged in part time work outside of the house.

DR. WRIGHT: Will you bring in the patient? (*Patient comes in.*)

DR. WRIGHT: How are you feeling?

PATIENT: All right.

DR. WRIGHT: Are you able to do your housework?

PATIENT: With help.

DR. WRIGHT: Do you wash your dishes?

PATIENT: Oh, yes!

DR. WRIGHT: Make the beds and sweep the floors?

PATIENT: Yes.

DR. WRIGHT: I hope that you do not move heavy furniture?

PATIENT: No.

DR. WRIGHT: Do you do your shopping?

PATIENT: Yes.

DR. WRIGHT: Do you have to walk up to your apartment?

PATIENT: One flight.

DR. WRIGHT: Do you have any trouble doing that?

PATIENT: No.

DR. WRIGHT: Thank you very much for coming. (*Patient leaves.*)

This patient presents a most interesting set of problems. One of these is the question, which is often presented, whether all patients with auricular fibrillation should be placed on anticoagulant therapy. We have taken the position that, with anticoagulant therapy as complicated as it is, it is probably not advisable. If anticoagulant therapy becomes very much simpler it may be acceptable. The reason that we do not recommend anticoagulant therapy for all cases is that many patients have auricular fibrillation for 15 or 20 years and never have an embolus. The chances are they will at sometime, but many do not. We do advise this therapy for patients in fibrillation with a history of one or more emboli. Even a single embolus may be a doubtful indication. The only difficulty with this type of reasoning is that the first embolus may be a very serious one which produces a permanent hemiplegia or results in the loss of a leg. Therefore, we are not on very firm ground. On the other hand, the difficulties and economics involved in keeping patients for years on anticoagulants when they may never have a thromboembolic episode are to be given serious consideration. At present if the patient has had two emboli or more, it seems as though long-term therapy is indicated. One embolus may be a sufficient indication, but without any emboli I doubt that we are justified in using anticoagulants. This must, however, rest with the discretion and judgement of the physician who is caring for the patient.

The second point of particular interest with this patient is this question of the renal embolus: an embolus to the renal artery with what appears to have been a restoration of function! Following severe pain in the flank there was no evidence of function in the right kidney. In this patient that was fairly strong evidence in favor of an interference with the arterial circulation, and gradually the function of the kidney was restored. It is now known that anticoagulant therapy does encourage the early restoration of the patency of vessels blocked by clots. This was not understood a few years ago, but the work of Helen Payling Wright in London[8] demonstrates that there is no doubt about this, especially if anticoagulants are administered shortly after a clot is formed or even before, when the clot has not become very firmly fibrosed. It is felt that this is not due solely to the action of the anticoagulants, but rather that these drugs allow the enzymes in the blood to act upon the clot directly.

DR. JERROLD LIEBERMAN: When patients with rheumatic or other heart disease eventually go into heart failure there is some change in liver function and at this time it is usually quite important to watch the anticoagulant dosage very carefully.

DR. WRIGHT: That is correct. This is also true especially if a patient has an episode, either in terms of embolism or myocardial infarction, which results in shock which, in turn, may produce changes in both liver and renal function. In such a patient small doses of anticoagulants may produce exaggerated elevations of the prothrombin time. The physician must be alert to these possibilities.

DR. SYMONS: Is there ever any trouble from menstrual irregularities arising during anticoagulant therapy?

DR. WRIGHT: In normal women I should say rarely, if ever; but we have uncovered a number of pathologic conditions of the cervix and uterus such as polyps, erosions and even carcinoma because the patient at a fairly satisfactory level of prothrombin time bled unexpectedly. It might be pointed out that this constitutes a signal for investigation, wherever

the bleeding may come from in the body. We have detected a number of cases with carcinoma of the bowel, ulcer of the bladder hitherto unsuspected, duodenal ulcers, and, as I said, lesions of the uterus because bleeding occurred at what might be called routine therapeutic levels. Never assume that such bleeding is due to the anticoagulant alone, but be certain that the patient does not have a lesion which the thrombosing mechanism of the body was formerly preventing from bleeding. When that protection was removed by the use of anticoagulants, bleeding became possible. This is a very important consideration because of the number of patients in whom the physician will be able to detect real pathology which hitherto had been missed.

DR. HUEBNER: Dr. Wright, in your opening discussion, you mentioned two uses for anticoagulants where the indications were not clearly defined, the recurrence of severe angina and cerebral spasm. I wonder if we might not add to that group those elderly patients with arteriosclerosis obliterans of the lower extremities who are having progressive occlusive episodes in the arteries. Some of them have impending gangrene of the toes or feet.

DR. WRIGHT: I think they might be well included, at least with a question mark. Many of them have their occlusions practically entirely on the basis of atherosclerotic plaques, but the final step is almost always a thrombus that develops in the narrowed lumen.

Conclusion. We have indicated that there are many unanswered questions regarding long-term anticoagulant therapy and that it does not lend itself to the precise statistical analysis which was used for a six weeks' study under controlled conditions for myocardial infarction. Nevertheless there is increasing evidence that for some patients it represents the only hope of preventing or treating devastating continuing disability, and it may delay or prevent a fatal conclusion due to a thromboembolic episode.

REFERENCES

[1] NICHOL, E. S., AND FASSETT, D. W.: An attempt to forestall acute coronary thrombosis: preliminary note on the continuous use of Dicumarol. South. M. J. **40:** 631, 1947.

[2] SPRAGUE, H. B., AND JACOBSEN, R. P.: A case of rheumatic heart disease with periodic arterial embolization. Ambulatory treatment with Dicumarol. M. Clin. North Amer. **32:** 1309, 1948.

[3] COSGRIFF, S. W.: Prophylaxis of recurrent embolism of intracardiac origin. J. A. M. A. **143:** 870, 1950.

[4] ASKEY, J. M., AND CHERRY, C. B.: Thromboembolism associated with auricular fibrillation. Continuous anticoagulant therapy. J. A. M. A. **144:** 97, 1950.

[5] TULLOCH, J., AND WRIGHT, I. S.: Long-term anticoagulant therapy, further experiences. Circulation **9:** (June) 1954.

[6] WRIGHT, I. S., BECK, D. F., AND MARPLE, C. D.: Myocardial infarction and its treatment with anticoagulants. Lancet **1:** 92, 1954.

[7] OVERMAN, R. S., STAHMANN, M. A., AND LINK, K. P.: Studies on the hemorrhagic sweet clover disease, VIII. The effect of 2-methyl-1,4-naphthoquinone and 1-ascorbic acid upon the action of 3,3′ methylenebis (4-hydroxy-coumarin) on the prothrombin time of rabbits. J. Biol. Chem. **145:** 155, 1942.

[8] WRIGHT, H. P.: Influence of anticoagulant therapy on rate of recanalisation of experimental thrombosis of veins. Brit. J. Surg. **40:** 163, 1952.

CLINICAL PROGRESS

Editor: HERRMAN L. BLUMGART, M.D.

Associate Editor: A. STONE FREEDBERG, M.D.

Medical Aspects of Patients Undergoing Surgery for Mitral Stenosis

By LEWIS DEXTER, M.D., LAWSON MCDONALD, M.D., MURRAY RABINOWITZ, M.D., GEORGE A. SAXTON, JR., M.D., AND FLORENCE W. HAYNES, PH.D.

THE ADVANCE of cardiac surgery has made necessary the revision, in recent years, of many views on rheumatic heart disease. If the mitral valve is affected, it is now most important to determine whether mitral stenosis is mild or severe and whether it is the main cause of the patient's disability if other valvular lesions are present.

During the last four years, the authors and their colleagues have supervised the selection and medical management of approximately 600 patients undergoing surgery for mitral valve disease by Dr. Dwight E. Harken. This report embodies the experience gained. In many aspects it reflects combined medical and surgical opinion and in others only that of the authors; it is certainly not to be regarded as final or unequivocal. The subject must be constantly under revision as further experience accumulates. Since this report deals entirely with our own experience, the bibliography is limited. For a wider perspective, the reader is referred to the first seven articles listed in the references.

A brief review of the pathologic physiology of mitral stenosis will first be presented, in an attempt to explain the hemodynamic basis of the clinical syndromes found.

From the Medical Clinic, Peter Bent Brigham Hospital, and the Department of Medicine, Harvard Medical School, Boston, Mass.

This work was supported by grants from the Life Insurance Medical Research Fund and the National Heart Institute, U. S. Public Health Service (Grant No. H-450).

Dr. McDonald is a Rockefeller Travelling Fellow in Medicine.

Dr. Rabinowitz is a Fellow of the National Heart Institute, U. S. Public Health Service.

PATHOLOGIC PHYSIOLOGY OF MITRAL STENOSIS[8]

In the absence of active rheumatic carditis, the symptoms resulting from mitral stenosis appear to be largely due to the mechanical obstruction to the flow of blood through the mitral valve, with or without additional precapillary obstruction in the lungs. The normal mitral valve is pliable and has an orifice of 4 to 6 sq. cm., and at rest about 6 liters of blood per minute pass through it during diastole. The orifice of the normal valve is large enough to permit this flow with a pressure gradient from left auricle to left ventricle of only 1 or 2 mm. Hg during early diastole.

As the mitral valve becomes stenotic, the pressure in the left auricle must rise if a normal blood flow is to be maintained. Since no physiologic barrier exists between the left auricle and the pulmonary capillaries, elevations of pressure in the auricle are accompanied by similar increases of pressure in the pulmonary veins and capillaries. Pulmonary capillary pressure cannot long exceed the osmotic pressure of plasma without the transudation of fluid and the occurrence of pulmonary edema. Although 25 mm. Hg is usually considered to be the level of the osmotic pressure of plasma, the critical upper limit to which the pulmonary "capillary" pressure can rise, if the patient is to remain free from pulmonary edema, has actually been found to be approximately 30 mm. Hg. Cardiac output falls concomitantly with narrowing of

the mitral valve; the pulmonary "capillary" pressure is thus enabled to remain at subcritical levels in the presence of an extremely small valve. The main effects of stenosis of the mitral valve are, therefore, a rise of pressure from a normal of about 15 to about 30 mm. Hg proximal to the valve and a modest decrease of the amount of blood flowing through the valve.

When the mitral valve approaches 1.0 sq. cm. in size, there is an increase in the resistance to the flow of blood through the precapillary vessels in the lungs. The origin of this may be functional or organic due to intimal proliferation and medial hypertrophy of the small vessels. Both factors may be present.[9] The exact pathogenesis of these changes is unknown. We have not observed an elevated pulmonary arteriolar resistance, however, until the resting pulmonary "capillary" pressure is 20 mm. Hg or more at rest, and we have assumed that the stimulus for the appearance of this increased resistance is a state of chronically impending pulmonary edema. There is great individual variation in the rapidity of onset and in the severity of this vascular change. Some patients never seem to develop it, and in others, it appears to develop, pari passu, with the stenosis.

With the superimposition of increased pulmonary vascular resistance, the pulmonary arterial pressure progressively rises, and in severe cases it may be considerably higher than the systemic arterial pressure. Confronted with an enormously increased work load, the right ventricle hypertrophies, and may dilate and fail in its attempt to maintain a flow of blood against these two resistances (mitral and pulmonary vascular).

The cardiac output falls as the total pulmonary resistance rises; in extreme cases it may drop to 2 liters per minute. With such a reduction of cardiac output, the mitral valve may reach a very small size without necessitating a further rise of left auricular and pulmonary "capillary" pressures. Valve orifices as small as 0.3 sq. cm. have been seen, post mortem, in extreme cases.

The pulmonary vascular process appears to protect the lungs from pulmonary edema in two ways. The first is through the reduction of cardiac output which, on exercise, rises little if any.[10] The second, as emphasized recently by Araujo and Lukas[11] is that the pulmonary edema threshold in patients with an elevated pulmonary vascular resistance is at a pulmonary "capillary" pressure of about 35 mm. Hg. Our experience is in accord with this observation. Estimation of the plasma proteins in these patients indicates that the osmotic pressure of plasma is probably not increased. It is difficult to conceive of an increased permeability to the passage of fluid across capillary endothelium to alveoli, but the rate at which fluid crosses this barrier may well be slowed due to the thickening of the capillary basement membrane and the widening of the interstitial space between the capillary and alveolar membrane.

Clinical Findings in Mitral Stenosis

In the natural history of mitral stenosis, the first attack of acute rheumatic fever typically occurs in the first two decades. A relatively asymptomatic period follows until 35 to 45 years of age, when disability first appears. Thus, about 20 years usually elapse between the onset of acute rheumatic fever and critical narrowing of the mitral valve. In some cases, the time lag may be only a few years, and in others the valvular stenosis is never sufficient to produce symptoms.

The clinical manifestations of mitral stenosis vary with the degree of narrowing of the mitral valve and with the severity of complicating pulmonary vascular resistance.[12] Considerable anatomic stenosis of the mitral valve can be present without symptoms. Eventually, the elevation of pressure which it produces in the pulmonary circuit is associated with the production of severe respiratory symptoms. At a valve size of 2 sq. cm., the pulmonary "capillary" pressure is little elevated at rest, although it may rise with vigorous exercise. Mild dyspnea on exertion does not usually appear until the mitral valve is about 1.5 sq. cm. At a valve area of 1.0 sq. cm. the resting pressure in the pulmonary "capillaries" and left auricle is usually about 20 mm. Hg; this quickly rises to pulmonary edema levels with the slightest exertion. The right ventricle hypertrophies, dilates and fails only *after* the appearance of an increased pulmonary vascular resistance.

The clinical signs of mitral stenosis include a small pulse, a discrete apex impulse, a loud apical first heart sound and a rumbling mitral diastolic murmur. It should be emphasized that although the murmur is of great diagnostic value, it does not unequivocally indicate the presence of mitral stenosis. Cases with rumbling apical diastolic murmurs have been observed in patients with auricular septal defect, Eisenmenger's syndrome, patent ductus arteriosus, thyrotoxicosis, constrictive pericarditis, hemochromatosis, and certain other forms of diffuse myocardial disease in which, at autopsy, there has been no abnormality of the mitral valve. Therefore, caution must be exercised in drawing conclusions from a murmur alone. Conversely, in the early, clinically insignificant stage of mitral stenosis, and occasionally in the late stages, no diastolic murmur may be audible.

The radiologic demonstration of calcification of the mitral valve is a helpful confirmatory diagnostic finding. Electrocardiographic and other radiological findings will be considered later. A diagnosis of mitral stenosis cannot be made by venous catheterization, although when the diagnosis is already clinically established, this technique may aid in determining its severity. Pulmonary "capillary" pressure is elevated in both mitral stenosis and left ventricular failure. Although a slow run-off time of the V-wave of the pulmonary "capillary" pressure pulse is suggestive of mitral stenosis, we have not found this to be reliable. At catheterization, the diagnosis of mitral stenosis can be made only by simultaneous recording of the pulmonary "capillary" pressure, with a venous catheter, and the left ventricular diastolic pressure, with an arterial catheter introduced into the left ventricle. The latter is, however, not recommended as a routine procedure. When the mitral valve is of adequate size, a barely measurable difference in pressure exists between the left auricle and left ventricle during diastole. Mitral stenosis or some physiologically similar lesion such as tumor or thrombus in the left auricle, or pulmonary venous thrombosis (of which we have seen one case) is present when the pulmonary "capillary" pressure is higher than the left ventricular diastolic pressure.

Clinical Syndromes in Mitral Stenosis

In determining the severity of mitral stenosis, it is necessary to take into account any aggravating factors which may superimpose an additional burden to the mitral and pulmonary vascular obstructions. Pregnancy, thyrotoxicosis, intercurrent infections, pulmonary embolism, uncontrolled tachycardia, paroxysmal arrhythmias, and active rheumatic carditis are examples. When such complications are present, the patient may appear to be in extremis, and yet become asymptomatic after their disappearance. In assessing the severity of the mitral stenosis itself, attention must be focussed on the manifestations when these complications are absent.

Our observations indicate that in the natural history of mitral stenosis four syndromes, representing different stages of the disease, can be clinically defined.[12] To facilitate the selection of patients for surgery and to evaluate the severity of the stenosis, classification of patients into these syndromes has been found to be advantageous, although often the individual patient will be found to be in some intermediate stage. In some, a history may be obtained of their having passed through previous stages.

Stage 1. No increased pulmonary vascular resistance and subcritical narrowing of the mitral valve (orifice greater than 1.2 sq. cm.)

Stage 2. Little or no increase of pulmonary vascular resistance and critical narrowing of the mitral valve (orifice less than 1.2 sq. cm.)

Stage 3. Moderate increase of pulmonary vascular resistance (6 to 10 times normal) and further narrowing of the mitral valve (1.0 sq. cm. or less).

Stage 4. Severe degree of pulmonary vascular resistance (more than 10 times normal) and severe narrowing of the mitral valve (0.8 sq. cm. or less).

Stage 1. Patients in this group have no increase in pulmonary vascular resistance and a mitral valve which is greater than 1.2 sq. cm. Often it is not until the valve is about half the normal size of 4 to 6 sq. cm. that patients notice shortness of breath, and then only on violent exertion. They may become unduly tired at the end of a long day of strenuous work, presuma-

bly on the basis of a suboptimal cardiac output. Usually patients automatically refrain from strenuous exercise or prolonged exertion as the mitral stenosis progresses. Therefore, they are liable to have few if any symptoms until the valve becomes so reduced in size that activities, which are considered essential for a normal life, can no longer be maintained. When the mitral valve is between 1.2 and 1.5 sq. cm., breathlessness on moderate exertion is usually noticed. As activities are reduced within the bounds of symptoms, the patient may have no symptoms except under some circulatory strain such as intercurrent infections, bouts of tachycardia, pregnancy, and other conditions which overload the circulation. The left auricle may be enlarged on fluoroscopy, but electrocardiographic and radiologic evidence of right ventricular hypertrophy are absent.

Stage 2. Stage 2 includes patients who have developed little or no increase of pulmonary vascular resistance but who have a mitral valve area of 1.2 sq. cm. or less. Although the patient may be comfortable at rest, severe pulmonary symptoms appear with mild exertion, emotion, or tachycardia. The valve has narrowed to a critical level, and even resting pressures in the pulmonary capillaries are near the threshold of pulmonary edema. The normally functioning right ventricle can increase its output without difficulty, but any additional flow of blood through the stenosed mitral valve readily results in a rise of pressure in the left auricle and pulmonary circuit, the accumulation of blood in the lungs, and the formation of pulmonary edema. In this stage, the patient cannot climb more than a flight of stairs without gasping for breath. Orthopnea, paroxysmal nocturnal dyspnea, attacks of acute pulmonary edema, and hemoptyses of gross amounts of bright red blood frequently occur. These individuals run a stormy course and are of the type described by Bland and Sweet[13] as "tight mitral stenosis" with a normal-sized heart. Electrocardiographic and radiologic evidence of right ventricular enlargement may or may not be present.

Stage 3. This stage is characterized by a pulmonary vascular resistance which is 6 to 10 times the normal, and by a mitral valve orifice which is 1 sq. cm. or less in size. Patients in this group may or may not have passed through the clinical syndromes described in stages 1 and 2. Although many patients in this group still suffer from considerable dyspnea, in some it appears to be masked by fatigue, as a genuine symptom of organic disease. The activity of these patients is much curtailed, and some may experience difficulty in explaining their symptoms because of their essentially negative nature. They simply do not "feel up to par" and complain of being tired and fatigued. They may appear as malingerers or victims of cardiac neuroses, and indeed on many occasions it may be difficult to decide how much of the symptomatology has such an origin and how much is real. However, patients in this group have a severe physiologic abnormality as the cause of such symptoms—a low cardiac output.

The electrocardiogram practically always shows right ventricular hypertrophy, provided that this is not masked by left ventricular hypertrophy due to other complicating lesions. Radiologically, there is enlargement of the left auricle, right ventricle and pulmonary artery. Generalized cardiac enlargement of more than 20 per cent is almost always present.

Stage 4. Patients in this group have a pulmonary vascular resistance which is 10 times the normal or more and a mitral valve orifice which is usually less than 0.8 sq. cm. These terminal patients use every compensation which the body can muster. Thus, the pulmonary "capillary" pressure at rest is always greatly elevated, and the cardiac output extremely low. The pressure in the pulmonary artery rises to great heights in an attempt to overcome the areas of high resistance in the lesser circulation. The right ventricle may fail due to its great pressure load.

The main symptoms of patients in stage 4 are dyspnea, orthopnea and paroxysmal nocturnal dyspnea due to the fact that these patients are on the verge of pulmonary edema at all times. The cardiac output is even lower than in stage 3 and is accompanied by exhaustion, fatigue, and complete physical incapacity. Respiratory symptoms, however, are always more distressing to the patient than a sense of fatigue. Loss of weight and cachexia are common, and the patient is usually bedridden or

nearly so. Signs of right ventricular failure are frequently found. Generalized cardiac enlargement, 50 per cent or more greater than normal, is usual. The right ventricle is huge, the left auricle moderately or extremely enlarged, the pulmonary artery very prominent, and pulmonary vascular markings increased. The electrocardiogram always shows evidence of right ventricular hypertrophy.

The majority of patients with pure mitral stenosis fit into one or another of these stages; the remainder have features of various stages or represent a gradation between them. In certain individuals the cardiac output does not fall even with severe mitral stenosis. If this greater flow through the narrowed mitral valve is to be maintained, a higher left auricular and pulmonary capillary pressure is needed and respiratory symptoms are more severe. On the other hand, some patients lower their outputs excessively. They do very well in the sense that they have few respiratory symptoms, but they tire easily. Such variations show that although a close relation exists between the underlying physiologic abnormality and the clinical, electrocardiographic and radiological findings, the relation is not absolute.

Indications for Surgery

Those who have to select patients for mitral surgery should reflect on certain fundamental problems.

1. What does surgery accomplish? In skilled hands, the operation results in a widening of the stenotic valve without the production of mitral insufficiency. In the majority of cases valves can be increased in size to about 1.5 to 2 sq. cm.[9] Nature has been prodigal in the size of the normal mitral valve, and an orifice of 1.5 sq. cm. or more, which is only one-third of the normal, is compatible with practically normal activity. Over the course of six to eight months, the increased pulmonary vascular resistance returns to normal or nearly normal following successful mitral valve surgery. Right ventricular function improves as the pressure in the lung falls.

The ability to climb a flight of stairs at a normal rate without symptoms is the equivalent of leading an essentially normal life. Thus, if a patient is able to perform this amount of activity, he can earn a livelihood, although he must refrain from occupations which involve heavy physical labor; a woman can raise children, go marketing, and do all but the heaviest type of housework. Our experience has been that this is what is almost uniformly accomplished by surgery for mitral stenosis.

2. Will surgery improve in the future? There is every reason to think that in years to come the present surgery for mitral stenosis will be considered blind; the surgeon depends upon his finger, instead of his eyes, to delineate the abnormal anatomy. If an extracorporeal pump or the use of hypothermia is sufficiently developed, surgery of the mitral valve may in the future be much more effectively performed under direct vision.

3. What is the risk of surgery? This primarily depends upon the stage of the disease. In stage 1 (groups 1 and 2, New York Heart Association classification), with which the authors have had no experience, it is reasonable to assume that the mortality would be very low. In stages 2 and 3 (group 3, New York Heart Association classification) the mortality has been about 3 per cent in the hands of Dr. D. E. Harken. In stage 4 (group 4, New York Heart Association classification) the mortality has been 23 per cent.

4. What would the patient's course be without surgery? This is highly variable, and generalizations cannot be made. Patients who have shown a progressively downhill course should be considered candidates for surgery, whereas those who have been in a relatively static and asymptomatic state may never require it. It is well recognized that a certain number of patients with mitral stenosis will live a normal life span. This is sufficient reason to discourage the idea of operating on "murmurs" alone (stage 1).

It is concluded that the indication for surgery is the presence of the clinical syndromes described above in stages 2, 3, and 4 of the disease (corresponding to groups 3 and 4 of the New York Heart Association classification).

In addition, the occurrence of arterial embol-

ism should be regarded as an indication for surgery, whether or not cardiac incapacity is present. Prophylactic anticoagulation therapy is unsatisfactory and auricular appendectomy alone is inadequate because only about half of left auricular thrombi occur in the appendage.[14] Arterial embolism after successful surgery for mitral stenosis is rare, even in those cases who have had repeated embolism preoperatively. There is, however, a small but definite risk of embolism during surgery.

Other Considerations in Selecting Patients for Surgery

1. Age

In the majority of patients under the age of 20 years, disability stems from active rheumatic carditis and not from a critically narrowed mitral valve. Surgery is therefore not generally advocated for these individuals. Occasionally significant narrowing of the valve can occur in childhood, but it is exceptional. None of our cases undergoing surgery have so far been under the age of 18 years.

Surgery has been performed on a number of patients in their fifties and sixties; the oldest who made a good recovery was 69 years of age. Although these patients are poorer operative risks than those who are younger, some of the best results have been in patients over the age of 50 years. Advancing age, in itself, does not appear to be a contraindication to operation if otherwise the indications are clear.

2. Mild Cases

We believe that patients who are in stage 1 (groups 1 and 2 of the New York Heart Association classification) should not be subjected to operation, even though a degree of anatomic stenosis may be present. It is considered at present to be in the patient's interest to postpone surgery until such time as the technique is so improved that the risk is negligible, or until the patient progresses to stage 2 (groups 3 or 4 of the New York Heart Association classification).

3. Should Surgery be Withheld?

At times we have seen patients with such severe mitral stenosis that the operative risk has appeared inordinately high. Such patients have everything to gain and little to lose by surgery. Surgery has not been withheld in any patient with mitral stenosis because of the severity of the disease. The only question has been whether surgery will be beneficial to the individual. Following a period of rigid medical management, during which patients are brought to an optimal condition, surgery should be undertaken. In this severely ill group, the mortality has been 23 per cent, but on the other hand the salvage rate has been 77 per cent. Some of the most spectacular results have occurred in these individuals.

4. Complicating Diseases

A. Other Valve Lesions. The presence of valvular lesions other than mitral stenosis may present a considerable problem in evaluation, and an attempt must be made to determine the degree of disability which results from each. If mitral stenosis is the limiting lesion, operation is at present considered advisable, even though symptoms due to other lesions may later increase. This is because, first, the relief of mitral stenosis will alleviate severe symptoms for a period of years, and, second, when the other valvular lesions do produce symptoms, surgical techniques may have sufficiently improved for them to be treated. Evaluation of multivalvular disease is not simple. A brief resumé of the problem follows.

(1) Aortic Stenosis. Of all the valvular lesions, the authors find this the hardest to evaluate. Severe aortic stenosis may be accompanied by anginal pain, left ventricular failure, and syncopal attacks. Similar chest pain and pulmonary edema may occur in patients with mitral stenosis, and their source can be difficult to determine when both valvular lesions coexist. The intensity of the murmur or thrill in aortic stenosis has been of little value in determining the severity of aortic stenosis.

Aortic stenosis readily masks many of the characteristic manifestations of mitral stenosis, when the two lesions coexist. Dyspnea may be due primarily to the mitral stenosis or to the aortic stenosis if the left ventricle has failed. This is usually associated with marked enlargement of the left ventricle radiologically. The

electrocardiogram reveals left ventricular hypertrophy, even with mild aortic stenosis, and the presence of right ventricular hypertrophy due to mitral stenosis may be masked. In these cases, marked enlargement of the pulmonary artery points to an important degree of mitral stenosis. The left auricle is only slightly enlarged in patients with aortic stenosis alone.

Brachial arterial pressure tracings obtained by arterial puncture have been of some value in excluding aortic stenosis as a significant lesion. The duration of the systolic upstroke, that is, the interval from the onset of upstroke to the peak of systole, is normally equal to 1 divided by the square root of the pulse rate, or about 0.11 second at a pulse rate of 80.[15] Various conditions, including aortic stenosis, hypertension, and coarctation of the aorta, may be associated with a prolonged upstroke. The duration of upstroke is also influenced by the cardiac stroke output. If, however, the duration of upstroke is normal in ill individuals who have the murmurs of mitral and aortic stenosis, it can be inferred that the aortic stenosis is functionally insignificant and surgery of mitral stenosis will be beneficial. The degree of prolongation of the systolic upstroke appears to be only roughly related to the severity of aortic stenosis when it is due to that lesion.

(2) Aortic Regurgitation. Many patients with mitral stenosis have associated aortic regurgitation. It should be noted, however, that it may be hard to distinguish the murmurs of aortic and pulmonary regurgitation. The level of the diastolic blood pressure has served as the most useful single measurement in determining the severity of aortic regurgitation. Since the diastolic blood pressure normally varies considerably with the state of the patient, it is essential that basal readings are obtained on several occasions. If the resting diastolic pressure is maintained at 50 mm. Hg or greater, it has been concluded that aortic regurgitation is clinically insignificant. If the diastolic blood pressure is between 30 and 50 mm. Hg, the aortic regurgitation is of borderline severity. When the diastolic pressure is below 30 mm. Hg the regurgitation has been considered to be thoroughly significant and surgery of co-existing mitral stenosis has not been advocated.

(3) Mitral Regurgitation.[16] In the past, mitral regurgitation has been somewhat neglected by physicians. With the advent of cardiac surgery, it is assuming its true place of importance.

The problem is that of determining which lesion is the predominant one in the production of the patient's symptoms when both stenosis and regurgitation are present. The presence of an apical systolic murmur is of some value, but caution must be assumed in its interpretation. Significant mitral regurgitation has been observed in the absence of an apical systolic murmur, and murmurs as loud as grade 3 and 4 have been heard without significant mitral regurgitation. As a general rule, however, the loudness of the apical systolic murmur, if it is of grade 3 or more intensity, usually bears a rough relation to the severity of the lesion. The first sound at the apex is usually muffled in mitral regurgitation; in mitral stenosis it is accentuated.

Anatomically and functionally, mitral stenosis is often a pure lesion, but mitral regurgitation is almost always associated with some degree of anatomic, although not necessarily functionally significant, stenosis.[17] As the mitral valve narrows due to stenosis, a progressively smaller volume of blood can flow through it without the left auricular pressure rising above the level at which pulmonary edema occurs. With mitral regurgitation, the amount of blood which flows through the mitral valve is increased over peripheral flow. If mitral regurgitation is present, more blood must flow through the mitral orifice if the same aortic output is to be maintained. Therefore, severe mitral regurgitation and severe stenosis are incompatible, and at most only mild regurgitation can coexist with a mitral valve area of less than 1.0 sq. cm. Regurgitation of mild or moderate degree can be present with a valve size of 1.2 to 1.5 sq. cm. and it can be mild, moderate, or severe with one in excess of 1.6 sq. cm.

Three stages of severity of mitral regurgitation can be distinguished.

(a) *Mild mitral regurgitation* is an asymptomatic lesion and of no functional significance except insofar as it can aggravate the symptoms of mitral stenosis by increasing mitral valve

flow. The clinical course and manifestations are those of mitral stenosis previously described. In such cases, surgical relief of the stenosis is highly effective in relieving symptoms.

(b) *Moderate mitral regurgitation* is physiologically characterized by a low cardiac output, relatively good left ventricular function, and no pulmonary congestion. In these individuals there is absent or minimal exertional dyspnea but as a result of the low cardiac output they easily become fatigued. The electrocardiogram may show evidence of left, combined, or no ventricular hypertrophy, but *not right ventricular hypertrophy alone*. On x-ray examination, the left auricle is at least moderately enlarged and is often huge, and left ventricular enlargement may be apparent. There may be right ventricular enlargement as well. The pulmonary artery is not prominent, either in the posteroanterior or oblique views and the hilar vessels are unlikely to be congested. This group of patients may be easily confused with patients in stage 3 of mitral stenosis because of their chronic exhaustion. Although symptoms and physical signs may be similar, radiologic and electrocardiographic findings are different. These individuals have mitral regurgitation as the predominant lesion, the mitral stenosis not being functionally significant. Surgical relief of whatever anatomical stenosis they may have does not alter their disability.

(c) With *severe mitral regurgitation*, the left ventricle fails and pulmonary congestion results. Dyspnea and orthopnea are the predominant complaints of these patients; breathlessness overshadows cachexia, exhaustion, and weakness. Physical examination, radiologic and electrocardiographic findings are similar to those in patients with moderate regurgitation. They may be more marked, and signs of engorgement of the lungs and right ventricular failure may be present. These individuals can best be distinguished from those in stage 4 of mitral stenosis by the absence electrocardiographically of right ventricular hypertrophy alone and the lack of radiographic prominence of the pulmonary artery. Surgical widening of the mitral valve does not benefit them.

Laboratory measures, such as fluoroscopic observation of systolic expansion of the walls of the left auricle, electrokymography, roentgenkymography, esophageal pulse wave tracings, and direct left auricular tracings or pulmonary "capillary" pressure measurements are of limited value in ascertaining whether regurgitation or stenosis is the predominant lesion. Various factors may affect such measurements as the height of the "V"-wave of the pulmonary "capillary" tracing and systolic expansion of the left auricle. These include the pressure-volume characteristics of the left auricle and pulmonary venous compartment at the time of observation, the amount of pulmonary venous inflow and the degree of auricular distention, as well as the amount of blood regurgitated through the mitral valve.[17] For example, the regurgitation of 50 cc. of blood per beat into an auricle with a capacity of 1 liter may produce an immeasurable alteration in volume or pressure; a much smaller volume regurgitated into a tense, stretched chamber of moderate size can lead to impressive changes. Data from these procedures must be cautiously interpreted. Although a previous report[18] seemed to indicate systolic expansion of the left auricle fluoroscopically to be a useful technic of appraisal, our present belief is that at best it and the other methods mentioned may indicate the presence of mitral regurgitation, but frequently they fail to show its presence, and often they have been found to be of no help in estimating the severity of the lesion.

Cardiac catheterization is usually of little aid preoperatively for the same reasons. Only after surgery, when the size of the mitral stenotic orifice is described, can an estimate of the magnitude of the regurgitant flow in liters per minute and size of the regurgitant orifice in square centimeters be calculated.[17]

The clinical manifestations described above have been found to be the most reliable guide to the differentiation of predominant mitral stenosis from regurgitation. When both lesions coexist, the pattern of either stenosis or regurgitation will usually predominate. If the pattern is one of stenosis, benefit can be derived from surgery; if it is that of regurgitation, we have not observed benefit by operating for mitral stenosis.

(4) Pulmonic Stenosis. Rheumatic involvement of the pulmonic valve has not been encountered by the authors, and will not be further considered.

(5) Pulmonic Regurgitation. The Graham-Steell murmur of pulmonic regurgitation is not uncommon; it is best heard in the pulmonary area and is a soft early diastolic murmur transmitted down the left border of the sternum. It tends to disappear after successful mitral valve surgery, but otherwise it may sometimes be impossible to distinguish it from the murmur of aortic regurgitation.[19]

(6) Tricuspid Regurgitation. Tricuspid regurgitation is present in practically all patients with severe mitral stenosis, as judged by the configuration of the right auricular pressure tracing. It is impossible to differentiate between organic and functional tricuspid insufficiency; the latter is undoubtedly more common. In either case, its presence should not be considered a contraindication to surgery. If tricuspid regurgitation is functional and due to dilatation of the right ventricle, it may disappear completely as right ventricular function improves after mitral valve surgery. Even if organic regurgitation is present, it will be greatly reduced after operation, because the systolic pressure in the right ventricle falls and the amount of tricuspid regurgitation correspondingly diminishes.

(7) Tricuspid Stenosis. Although tricuspid stenosis is an uncommon lesion, at least in New England, several cases have been observed. The only certain method of recognizing tricuspid stenosis is by finding, at catheterization, a higher diastolic pressure in the right auricle than in the right ventricle. The relief of mitral stenosis may cause the manifestations of tricuspid stenosis to increase, because the subsequent increase in cardiac output demands a greater pressure in the right auricle and systemic veins to force the blood through the tricuspid valve. If both mitral stenosis and tricuspid stenosis are present, the surgeon should be prepared to operate on the tricuspid valve immediately after the mitral.

B. Rheumatic Activity. This condition presents a problem of great difficulty in the evaluation of adult patients. Most authorities believe that progressive narrowing of the mitral valve is due to repeated rheumatic activity rather than to cicatricial contracture. Aschoff bodies have been found in biopsies of the left auricular appendage at the time of operation in about 40 per cent of our patients.[20] Although there is considerable controversy as to the significance of Aschoff bodies and their relation to rheumatic activity, it seems justifiable to conclude that they indicate rheumatic activity until there is concrete evidence to the contrary. Only a small number of these patients with Aschoff bodies in the auricular wall have been suspected of having rheumatic activity, either clinically or as a result of special investigations, and their postoperative course has not usually been different from that of patients with negative biopsies.[21] It is important always to consider the question of rheumatic activity, and whether the patient's disability may be partly due to active carditis as well as to established mitral stenosis. If there is rheumatic activity and evidence of severe stenosis, it can be assumed that the patient will be better able to withstand the added burden of activity if the valve is widened. A number of cases with unequivocal clinical signs of rheumatic activity have been operated upon with satisfactory results. Thus, contrary to general opinion, rheumatic activity is *not* considered by us to contraindicate surgery providing the valve orifice is already severely stenosed, and operation is urgently indicated. However, surgery has not been performed in cases with florid rheumatic activity.

C. Subacute Bacterial Endocarditis. Subacute bacterial endocarditis is uncommon at the stage of the disease when patients are usually seen for assessment with a view to surgery. When present, it is an absolute contraindication to operation. How long surgery should be delayed following antibiotic therapy is not yet clear. Ideally, it might be desirable to wait for six months, but frequently the patient's condition will not allow such delay. It has been customary to operate after six weeks of medical treatment.

D. Recent Pulmonary Infarction. Frequently, a pulmonary infarct with its attendant disability precipitates a decision regarding surgery of the mitral valve. If operation was indicated

by the patient's condition prior to this complication, it seems wise to operate after two weeks of anticoagulant therapy.

E. Pregnancy. Pregnancy complicating mitral stenosis presents a problem in which surgical experience has so far been limited. Burwell and Ramsey[22] have recently discussed this problem. They point out that although mitral valve surgery can be performed during pregnancy, it is at the expense of an added risk, and advise that it should be reserved for those women who cannot continue pregnancy without severe hazard, and in whom for some reason termination is not acceptable. Mitral surgery is best done in the nonpregnant state.

F. Auricular Fibrillation. The majority of our patients have had auricular fibrillation preoperatively. It has introduced no additional surgical hazards except that it predisposes to left auricular thrombosis. An advantage is that the pulse rate is more easily controlled with digitalis than in those with normal sinus rhythm.

G. Calcification of the Mitral Valve. This is not a contraindication to surgery. The operative result may occasionally be disappointing due to difficulty in maintaining patency of the orifice despite good anatomic fracture of the commissures. Most cases, however, have been greatly improved.

H. Other Serious Disease. The severity of any associated disease must be estimated before mitral surgery is considered. If the prognosis for the associated disease is good, it seems wise to operate for mitral stenosis, but if not, surgery should not be undertaken. The case of a 26 year old girl with both Addison's disease and severe mitral stenosis may be cited as an example.[23] Therapy of the Addison's disease with hormone or sodium tended to produce pulmonary edema and salt restriction for her cardiac condition produced Addisonian crises. The only solution to the problem was operation. This was performed, and the patient had an uneventful convalescence. Her subsequent course has been most satisfactory.

Medical Preparation for Surgery

Time in Hospital before Operation. Patients should usually be in the hospital for five to seven days before operation. Their condition can then be assessed and a strict cardiac regimen instituted. For very ill patients, a longer period may be needed.

Diet. All patients are placed on a low salt diet, consisting of 200 mg. of sodium chloride a day.

Digitalis. All patients, whether fibrillating or in normal sinus rhythm, are digitalized prior to surgery. Patients with normal rhythm frequently begin to fibrillate 24 to 72 hours after operation. In those who are already digitalized, this is readily brought under control by the administration of 0.25 mg. of Digoxin intravenously every two hours for two or three doses, whereas otherwise it may be difficult quickly to control sudden fibrillation. The main theoretic objection to the digitalization of patients preoperatively is that it may increase myocardial irritability and increase the risk of arrhythmias at and after operation. In a group of about 50 patients to whom digitalis was not administered, we did not observe any reduction of myocardial irritability during surgery, nor was the incidence of postoperative auricular fibrillation reduced. The aim is to secure adequate digitalization before operation. Myocardial toxicity rarely occurs if digitalis folia is prescribed because of the prior appearance of gastrointestinal complaints, whereas these warning signs may be absent with the glycosides.

Diuretics. Mercurial diuretics are administered if indicated. It has not been our custom to administer diuretics within 48 hours of the time of operation. They may accentuate electrolyte upsets during and after operation and with dietary salt restriction may lead to serious salt depletion.

Quinidine and Pronestyl. These drugs are not administered prophylactically to reduce myocardial irritability during surgery because the poor myocardial contractility which they cause may be as much or more of a problem at operation. They are administered only during the operation in the treatment of ventricular ectopic beats or ventricular tachycardia.[24]

Cortisone and Corticotropin (ACTH). Our experience with these drugs is limited. Their efficacy to control low-grade rheumatic activity is, at present, questionable.

Medical Aspects of Surgery

The surgical and anesthetic aspects of mitral operations have been well described.[25, 26, 27] Facilities for electrocardiographic recording during the operative procedure enable the pulse rate, the appearance of arrhythmias, and signs of myocardial irritability to be noted. However, the heart may contract poorly despite a normal electrocardiogram, and the physician and the surgeon must work in a closely knit team with regard to any therapy at any particular moment. For poor contractility, the drugs of choice are calcium chloride and epinephrine; for auricular arrhythmias, Prostigmine; and for ventricular irritability, Pronestyl.[24] In the presence of poor contractility accompanied by multifocal ventricular premature beats, neither epinephrine nor Pronestyl are desirable. Perhaps the only drug which it is then wise to administer is calcium chloride. Alternatively, one can wait until one or other dysfunction becomes predominant and then cautiously administer whichever drug is indicated.

The problem of cerebral embolism at the time of operation has been adequately discussed elsewhere.[27] It should be noted that it occurs in 5 to 10 per cent of patients, regardless of preventive measures. It is one of the inevitable hazards of this type of surgery.

Postoperative Medical Management

Patients require special nursing supervision for several days postoperatively. A low salt diet is maintained throughout convalescence and after patients return home; salt may then gradually be added to the diet if their progress is satisfactory. The patient is encouraged to get up on the second or third postoperative day. On the fifth or sixth day, they usually feel much better, and by the tenth day they are eating well, strolling along the corridors, and wanting to go home. Patients who are more severely ill initially are slower to recover because of the tremendous circulatory and bodily readjustments which must take place. Work or any routine activities should not be resumed for at least two months. Subsequently, the patient may gradually increase his activities. Improvement may not be complete, or an essentially normal life resumed, for a year or more.

In many cases with auricular fibrillation, the digitalis dosage must be increased postoperatively in order to maintain a heart rate of less than 100. With the subsidence of fever, the rate usually falls in a few days to a normal level. The administration of digitalis must be preceded by an electrocardiographic recording whenever the possibility of digitalis toxicity exists. In the patients with fibrillation, digitalis is maintained unless they revert to normal rhythm.

In those patients with normal sinus rhythm, quinidine, 0.3 Gm. every six hours by mouth, is begun following operation, with the object of preventing auricular fibrillation. If auricular fibrillation does appear, digitalis should be continued.

Patients who develop auricular fibrillation postoperatively or shortly before operation sometimes later revert spontaneously to normal sinus rhythm. If they do not, between the tenth and fourteenth postoperative day, an attempt is made to revert them with quinidine by the technic described by Levine.[28] Although this is usually accomplished without difficulty, there have been occasional failures. After reversion, patients are maintained on quinidine, 0.3 Gm. four times a day for a month or six weeks.

Diuretics are seldom indicated in the postoperative period.

In the majority of our patients with mitral stenosis, total body water and sodium are greater than normal[29] despite good cardiac therapy. The usual postoperative electrolyte response to any form of major surgery[30] includes a negative nitrogen and potassium balance accompanied by a fall in the level of serum sodium, oliguria, and minimal urinary excretion of sodium. The fluid and electrolyte response to mitral surgery is an exaggeration of the normal but differs in that fluid is retained considerably in excess of sodium in the first few postoperative days.[29] With fluid intake of 3000 cc. or more daily, the serum sodium concentration may fall to 120 mEq. per liter or less. The administration of sodium chloride does not prevent or correct this hyponatremia. If there is a restriction of salt intake (2 Gm. per day plus an amount equal to that lost by chest drainage) and of fluid intake (1500 to 1800 cc. per day plus an

amount equal to that lost by chest drainage) the postoperative hyponatremia is less conspicuous. The salt and fluid intake may need to be increased above these levels under certain conditions such as high fever and very hot weather. After about five days, a normal fluid and electrolyte balance is usually restored and the above restrictions are no longer necessary.

In some cases, personality changes appear during the first postoperative week. These are usually minor and of no consequence, but in some instances frank psychosis (paranoia and other states) has appeared. Most have been transient and have spontaneously cleared in a few days, but a few have required psychiatric treatment. These emotional disturbances have been studied by Fox, Rizzo, and Gifford[31] and have been reported elsewhere. The operation has been considered more as a precipitating than as a specific cause for the emotional disturbances. The emotional reaction may coincide with the postoperative hyponatremia. Psychoses have more recently been observed in patients whose postoperative fluid and electrolyte patterns have remained within essentially normal limits as a result of the fluid and electrolyte management described above. Although electrolyte disturbances may possibly aggravate the emotional reactions, a causal relationship has not been demonstrated.

Postoperative pulmonary embolism is not uncommon especially in patients with advanced disability, but the routine use of anticoagulants is not merited. If fever, tachycardia, and a raised respiratory rate cause suspicion of pulmonary embolism, heparin should be given for at least 10 days, provided that no surgical contraindications exist.

Dyspnea, orthopnea, paroxysmal nocturnal dyspnea, and actual pulmonary edema are rarely seen postoperatively if adequate widening of the valve has been effected. Removal of the obstruction at the mitral valve results in an immediate fall of pressure in the left auricle and pulmonary capillaries.

The operation does not confer immunity to a recurrence of rheumatic activity, and a stormy postoperative course may be evidence of it. All patients should have permanent prophylactic treatment with antibiotics after operation.[32]

A long-term follow-up study on these patients is being carried out by Dr. L. B. Ellis. This should provide valuable information regarding the immediate and late benefits of operation.

REFERENCES

[1] Bland, E. F.: Surgery for mitral stenosis: A review of progress. Circulation **5:** 290, 1952.

[2] Baker, C., Brock, R. C., Campbell, M., and Wood, P.: Valvulotomy for mitral stenosis. A further report on 100 cases. Brit. M. J. **1:** 1043, 1952.

[3] Bailey, C. P., Bolton, H. E., and Redondo-Ramirez, H. P.: Surgery of the mitral valve. Surg. Clin. North America **32:** 1807, 1952.

[4] Wade, G., Werkö, L., Eliasch, H., Gidlund, A., and Lagerlöf, H.: The haemodynamic basis of the symptoms and signs in mitral valvular disease. Quart. J. Med. **21:** 361, 1952.

[5] Soulié, P., diMatteo, J., Tricot, R., and Moreau, L.: Commissurotomie pour rétrécissement mitral. Resultats, indications operatoires. Bull. et mém. Soc. méd. Hôp. Paris **68:** 871, 1952.

[6] Chavez, I.: Las indicaciones del tratamiento quirúrgico de la estenosis mitral á la luz de los datos clínicos y hemodinámicos. Arch. Inst. cardiol. México **23:** 1, 1953.

[7] Griffith, G. C., Miller, H., Cosby, R. S., Levinson, D. C., Dimitroff, S. P., Zinn, W. J., Oblath, R. W., Herman, L. M., Johns, V. J., Jr., Meyer, B. W., and Jones, J. C.: The selection and management of patients with mitral stenosis treated by mitral comissurotomy. Circulation **7:** 30, 1953.

[8] Gorlin, R., Haynes, F. W., Goodale, W. T., Sawyer, C. G., Dow, J. W., and Dexter, L.: Studies of the circulatory dynamics in mitral stenosis. II. Altered dynamics at rest. Am. Heart J. **41:** 30, 1951.

[9] Dexter, L., Gorlin, R., Lewis, B. M., Haynes, F. W., and Harken, D. E.: Physiologic evaluation of patients with mitral stenosis before and after mitral valvuloplasty. Tr. Am. Clin. & Climatol. A. **62:** 170, 1951.

[10] Gorlin, R., Sawyer, C. G., Haynes, F. W., Goodale, W. T., and Dexter, L.: Effects of exercise on circulatory dynamics in mitral stenosis. Am. Heart J. **41:** 192, 1951.

[11] Araujo, J., and Lukas, D. S.: Interrelationships among pulmonary "capillary" pressure, blood flow and valve size in mitral stenosis. The limited regulatory effects of the pulmonary vascular resistance. J. Clin. Investigation **31:** 1082, 1952.

[12] Lewis, B. M., Gorlin, R., Houssay, H. E. J., Haynes, F. W., and Dexter, L.: Clinical and physiological correlations in patients with mitral stenosis. Am. Heart J. **43:** 2, 1952.

[13] Bland, E. F., and Sweet, R. H.: A venous shunt for marked mitral stenosis. Tr. Am. Clin. & Climatol. A. **60:** 71, 1948.

[14] Jordan, R. A., Scheifley, C. H., and Edwards, J. E.: Mural thrombosis and arterial embolism in mitral stenosis. A clinicopathologic study of fifty-one cases. Circulation **3:** 363, 1951.

[15] Unpublished observations

[16] McDonald, L., Rabinowitz, M., Saxon, G. A., Jr., and Dexter, L.: Clinical physiological, and pathological findings in mitral stenosis and regurgitation. To be published.

[17] Gorlin, R., Lewis, B. M., Haynes, F. W., and Dexter, L.: Studies of the circulatory dynamics at rest in mitral valvular regurgitation with and without stenosis. Am. Heart J. **43:** 357, 1952.

[18] Elkin, M., Sosman, M. C., Harken, D. E., and Dexter, L.: Systolic expansion of the left auricle in mitral regurgitation. New England J. Med. **246:** 958, 1952.

[19] Spiegl, R. J., Long, J. B., and Dexter, L.: Clinical observations on patients undergoing finger fracture mitral valvuloplasty. I. Auscultatory changes. Am. J. Med. **12:** 626, 1952.

[20] Decker, J. P., Hawn, C. Van Z., and Robbins, S. L.: Rheumatic "activity" as judged by the presence of Aschoff bodies in auricular appendages of patients with mitral stenosis. I. Anatomic aspects. Circulation **8:** 161, 1953.

[21] McNeely, W. F., Ellis, L. B., and Harken, D. E.: Rheumatic "activity" as judged by the presence of Aschoff bodies in auricular appendages of patients with mitral stenosis. II. Clinical aspects. Circulation. **8:** 337, 1953.

[22] Burwell, C. S., and Ramsey, L. H.: Operation on the mitral valve and the management of mitral stenosis in pregnant women. Tr. A. Am. Phys. **66:** 303, 1953.

[23] Cited through the courtesy of Drs. G. W. Thorn, D. Jenkins, and J. C. Laidlaw.

[24] Spiegl, R. J., Long, J. B., and Dexter, L.: Clinical observations in patients undergoing finger fracture mitral valvuloplasty. II. Electrocardiographic observations. Am. J. Med. **12:** 631, 1952.

[25] Harken, D. E., Dexter, L., Ellis, L. B., Farrand, R. E., and Dickson, J. F., III: The surgery of mitral stenosis. III. Finger fracture valvuloplasty. Ann. Surg. **134:** 722, 1951.

[26] Wasmuth, C. E.: Anesthesia for mitral comissurotomy. Cleveland Clin. Quart. **20:** 346, 1953.

[27] Harken, D. E., Ellis, L. B., Dexter, L., Farrand, R. E., and Dickson, J. F., III: The responsibility of the physician in the selection of patients with mitral stenosis for surgical treatment. Circulation **5:** 349, 1952.

[28] Levine, S. A.: Clinical Heart Disease, ed. 4. Philadelphia, Saunders, 1951.

[29] Wilson, G., Edelman, I., Brooks, L., Myrden, A., Harken, D. E., and Moore, F. D.: Metabolic changes associated with mitral valvuloplasty. Circulation **9:** 199, 1954.

[30] Moore, F. D., and Ball, M. R.: The Metabolic Response to Surgery. Springfield, Thomas, 1952.

[31] Fox, H. M., Rizzo, N. D., and Gifford, S.: Psychological observations of patients undergoing mitral surgery. A study of stress. Psychosomatic Med. In press.

[32] Breese, B. B., Bellows, M. T., Fischel, E. E., Kuttner, A., Massell, B. F., Raumelkamp, C. E., Jr., and Schlesinger, E. R.: Prevention of rheumatic fever. Modern Concepts Cardiovasc. Dis. **22:** 158, 1953.

ABSTRACTS

Editor: SAMUEL BELLET, M.D.

Abstracters

DAVID I. ABRAMSON, M.D., Chicago
ARTHUR BERNSTEIN, M.D., Newark
RUTH CORTELL, M.D., New York
A. D. DENNISON, M.D., Indianapolis
CHARLES D. ENSELBERG, M.D., New York
ALFRED FROBESE, M.D., Philadelphia
BENJAMIN A. GOULEY, M.D., Philadelphia
RAYMOND HARRIS, M.D., Albany
J. RODERICK KITCHELL, M.D., Philadelphia
ALDO A. LUISADA, M.D., Chicago
MORTON H. MAXWELL, M.D., Los Angeles
VICTOR A. MCKUSICK, M.D., Baltimore
S. S. MINTZ, M.D., Philadelphia
MORTON J. OPPENHEIMER, M.D., Philadelphia
ALFRED PICK, M.D., Chicago
SEYMOUR H. RINZLER, M.D., New York
FRANCIS F. ROSENBAUM, M.D., Milwaukee
ELLIOT L. SAGALL, M.D., Boston
DAVID SCHERF, M.D., New York
JOHN B. SCHWEDEL, M.D., New York
CHARLES R. SHUMAN, M.D., Philadelphia
FRANKLIN SIMON, M.D., Newark
LOUIS A. SOLOFF, M.D., Philadelphia
RALPH M. TANDOWSKY, M.D., Hollywood
S. O. WAIFE, M.D., Indianapolis
MARTIN WENDKOS, M.D., Philadelphia
STANFORD WESSLER, M.D., Boston

CONGENITAL ANOMALIES

Steinberg, I., Dotter, C. T., and Lukas, D. S.: Congenital Absence of a Main Branch of the Pulmonary Artery. J. A. M. A. **152:** 1216 (July 25), 1953.

Ten cases of congenital absence of a main branch of the pulmonary artery have been reported in the literature. Postmortem diagnosis was made in seven instances. Surgical exploration was responsible for two diagnoses and in only one case was the diagnosis made prior to surgery or death. The two cases reported were at least suspected on clinical and routine radiographic examinations and were conclusively established by angiocardiography. Such a diagnosis may be suspected when a conventional roentgenogram of the chest reveals overdistention and mediastinal herniation of one lung with hypoplasia and diminished vascularity of the affected lung. Absence of a main pulmonary artery branch is conclusively demonstrated by angiocardiography.

KITCHELL

Van Loo, A., Pannier, R., Vnylsteek, K., D'Heer, H., Van Beylen, C., and Blancquaert, A.: Hemodynamic Study in Six Cases with Infundibular Pulmonary Stenosis. Acta Cardiol. **8:** 252 (Fasc. 3), 1953.

The authors report catheterization data and angiocardiograms of six instances of infundibular pulmonary stenosis found in cases of tetralogy of Fallot and in cases of intact ventricular septum with or without an atrial communication.

The diagnosis of an infundibular stenosis and its type can be determined by analyzing the pressure gradients during retraction of the catheter from the pulmonary artery into the right ventricle, and by observing the mobility and the curvature of the catheter tip while exploring the region of the infundibulum. Three types of infundibular stenosis are distinguished. In the first, the outflow tract of the right ventricle consists of a solid muscle mass with numerous sinusoid channels and the catheter usually cannot be advanced into the pulmonary artery. Angiocardiography is the best technic to demonstrate this type of malformation. In a second type in which a valvular stenosis is associated with an infundibular stenosis, two gradients of the systolic pressure are found during the retraction of the catheter. In a pure infundibular stenosis the systolic pressure in the infundibular segment and in the pulmonary artery are equal, and the diastolic pressure in the former is 4 to 8 mm. Hg lower than in the latter. An approximate estimation of the shape of the infundibular stenosis can be made from the type of transition from one pressure value into the other. This transition occurs suddenly when the infundibular channel is short and narrow, and more gradually when the entrance into the stenosis is wide and conical.

PICK

McKeown, T., MacMahon, B., and Parsons, C. G.: The Familial Incidence of Congenital Malformations of the Heart. Brit. Heart J. **15:** 273 (July), 1953.

The familial incidence of congenital heart disease of 431 affected individuals was determined by noting its occurrence in 342 younger sibs. Six sibs were affected, an incidence of six times normal (3.2 per 1000). The incidence in first cousins and in parents was insignificantly higher than normal. There were seven with dextrocardia of whom two had parents who were first cousins. The author believes this incidence of consanguinity supports the suggestion

that this anomaly may be inherited as a recessive.

SOLOFF

CONGESTIVE HEART FAILURE

Altschule, M. D.: Hazards in the Treatment of Cardiac Decompensation. New England J. Med. **248:** 493 (Mar. 19), 1953.

The author emphasizes that injudicious or erroneous application of therapy may have harmful effects in congestive heart failure. Among the less commonly recognized toxic effects of digitalis are mentioned diarrhea, visual disturbances, auricular fibrillation and slowing of the heart by vagal action which produces Stokes-Adams attacks. The opinion is expressed that the belief that bed rest, of itself, causes deep femoral phlebitis and subsequent pulmonary infarction is not securely founded in controlled observation. It is pointed out that in addition to the well-known untoward effects of morphine, this drug has a hypotensive effect, especially in patients who are tilted up with feet dependent. Morphine has also been found to inhibit mercurial diuresis. Oxygen in concentrations of 90 to 100 per cent may cause a decrease in the vital capacity when given continuously for 24 to 36 hours. Oxygen may also favor the development of atelectasis by washing nitrogen out of the alveoli, which will then collapse, if blocked by secretions, when the oxygen is absorbed. Sudden vasomotor collapse may also occur when patients who have been receiving high concentrations of oxygen suddenly resume breathing room air. Harmful effects of oxygen therapy may be precipitated by concentrations as low as 40 per cent in cor pulmonale. In this disorder anoxia rather than excess carbon dioxide acts as the respiratory stimulant. Relieving the anoxia with oxygen depresses respiration and leads to dangerous carbon dioxide retention which may cause coma or confusional psychoses. Excess oxygen dissolved in the plasma may result in a decreased amount of basic reduced hemoglobin in the venous blood with the result that tissue carbon dioxide retention occurs.

It is mentioned that rapid injection of aminophylline may cause such vasodilatation as to precipitate collapse or death. Slower but still unduly rapid injection of the drug may increase cardiac work and produce cardiac pain in patients with rigid coronary arteries by producing lesser degrees of peripheral arteriolar dilatation. Although the diuretic effect of ammonium chloride is of short duration, when used alone, it augments mercurial diuresis and prevents hypochloremia which may occur in patients receiving mercurial injections. Toxic accumulation of ammonium ion may occur with large doses such as 15 Gm. daily and acidosis of serious degrees may occur in patients with renal insufficiency. Mercurial diuretics may deplete the body of chloride, sodium or potassium. Chloride loss is remedied with ammonium chloride. Potassium loss may be minimized by administration of fruit juices. There is reason to believe that potassium loss accentuates digitalis intoxication. The major hazard of low-sodium diets and also of ion-exchange resins is excess sodium depletion. Anticoagulant drugs carry a greater risk in congestive failure because of the hepatic damage present. The application of venous tourniquets carries a number of hazards including shock, reduction in cutaneous blood flow with subsequent fever due to impaired heat dispersal and hyperpnea due to entry into the blood of lactic acid and carbon dioxide accumulations when tourniquets are released. The author concludes that except for digitalis all therapy for cardiac decompensation is symptomatic and does not improve cardiac function except indirectly. Therefore the many therapeutic measures may be harmful at times.

ROSENBAUM

Lewis, B. M., Houssay, H. E. J., Haynes, F. W., and Dexter, L.: The Dynamics of Both Right and Left Ventricles at Rest and During Exercise in Patients with Heart Failure. Circulation Research **1:** 312 (July), 1953.

Fourteen patients with cardiovascular disease primarily affecting the left ventricle were studied at rest and during brief exercise by the technique of cardiac catheterization. Depending on the amount of functional disability, one or more abnormalities occurred during exercise in the following sequence: increased pulmonary "capillary" and pulmonary artery pressure, increased right atrial pressure and decreased cardiac output. Definite impairment of left ventricular function was demonstrable even when right ventricular function was completely normal. The results are discussed in relation to the response of heart muscle to various degrees of stretch. On the basis of these data, it is concluded that symptoms of pulmonary congestion can best be explained on a "back pressure" basis.

MAXWELL

Lorber, V.: Energy Metabolism of the Completely Isolated Mammalian Heart in Failure. Circulation Research **1:** 298 (July), 1953.

The mechanism of failure in the completely isolated mammalian heart was reinvestigated. A simplified system employing cat hearts was used in which only the left heart was permitted to do work and undergo volume changes. In confirmation of others, the process of failure was found to be characterized by impairment of mechanical efficiency, with little or no impairment of total energy liberation as measured by oxygen consumption. This was so whether failure occurred at constant volume and declining load, or with dilatation and constant load; in both cases oxygen utilization paralleled diastolic volume while efficiency declined. It was concluded that under the conditions of the study heart muscle failure was characterized by an inability to convert

emical energy to mechanical work, and not by a lure to liberate chemical energy. Such experiental artefacts as acapnia and altered substrate d not appear to be incriminated. The results pport the relationship of initial fiber length and ergy liberation as an important generalization in rdiac function. Some apparent conflicts between is concept and recent clinical investigations are scussed.

MAXWELL

CORONARY ARTERY DISEASE

Wolff, L., Mathur, K. S., and Richman, J. L.: The Diagnosis of Posterior Myocardial Infarction. Am. Heart J. **46:** 21 (July), 1953.

During an investigation of the diagnostic accuracy of the vectorcardiogram, as compared with the electrocardiogram, in myocardial infarction, it was learned that posterior wall infarction diagnosed vectorcardiographically may not be so diagnosed electrocardiographically when the electrocardiogram discloses left bundle branch block, when the posterior infarct is small, located high on the posterior wall, is old, or is associated with acute anterior wall infarction. Old anterior wall infarction and left ventricular hypertrophy do not interfere with the development of the electrocardiographic signs of posterior infarction. The authors conclude that the vectorcardiogram appears to be superior to the electrocardiogram for the diagnosis of posterior myocardial infarction.

RINZLER

Enos, W. F., Holmes, R. H., and Beyer, J.: Coronary Disease Among United States Soldiers Killed in Action in Korea. J. A. M. A. **152:** 1090 (July 18), 1953.

This is a preliminary report on 300 autopsies performed on United States battle casualties in Korea. It is a description of the gross lesions found in the coronary arteries; a subsequent paper will discuss in detail the histology and such pertinent data as race, body build, and personal habits of the individual soldiers. The average age of the men in this group was 22.1 years. In 77.3 per cent cases some gross evidence of coronary disease was demonstrated varying from fibrous thickening to complete occlusion of one or more of the main branches. The exact locations of the lesions was at or near points of bifurcation of the vessels. The hemodynamics of the coronary circulation as modified by the anatomic variations of the coronary arterial tree are implicated as an important factor in the formation of plaques.

KITCHELL

Pollack, O. J.: Visceral Atherosclerosis in Rabbits and in Man. Geriatrics **8:** 135 (March), 1953.

Experimental conditions and anatomic alterations induced by intravascular injection of cholesterol resemble more closely the human disease than if cholesterol-atheromatosis is produced by feeding cholesterol to rabbits.

None of the six arguments applied against dietary induction of atherosclerosis in the rabbit can be used fully against intravascular injection of colloidal cholesterol. The digestive tract is being bypassed thus making irrelevant the fact that the rabbit is herbivorous. The amount of cholesterol introduced into the blood stream is relatively small. The degree of hypercholesteremia produced by injection is much nearer to the cholesterol levels of human beings with atherosclerosis than if rabbits are fed cholesterol. The alteration of visceral vessels of various caliber is seen frequently on cholesterol injection. Early vascular changes more closely resemble those of man, in as much as lipophages are oval shaped and do not protrude into the lumen, although they are seated in the endothelial intimal layer. Due to the rapidity with which damage results upon injection, initial hydropic swelling of the intima can be observed in the rabbit such as is seen in man where it very likely precedes deposits of cholesterol. Thus, intravascular injection of colloidal cholesterol offers a useful experimental approach to the study of atherosclerosis.

BERNSTEIN

ELECTROCARDIOGRAPHY, VECTORCARDIOGRAPHY AND BALLISTOCARDIOGRAPHY

Smyth, C. N.: Experimental Electrocardiography of the Fetus. Lancet **1:** 1124 (June 6), 1953.

Optimum technics for fetal electrocardiography are described. In "more than 100 patients" the fetal QRS was recognized in all except two and in these the fetus was dead. In an addendum the author reports on energy-frequency analyses of fetal vs. adult QRS complexes. Whereas the maximum for adults is in the 10 to 20 cycles per second range, that for the fetal and newborn heart is in the 20 to 40 cycles per second range. The frequency response of his electrocardiograph is adjusted to cut off below 30 cycles per second. The author illustrates a case of congenital extrasystoles detected both *in utero* and in the neonatal period.

MCKUSICK

Toyoshima, H., Yamada, K., Itatu, H., and Mizuno, Y.: Relationship between the Intrinsic or Intrinsicoid Deflection and Time of Arrival of Activation by Unipolar Lead. Nagoya J. Med. Sci. **15:** 201 (Dec.), 1952.

The authors recorded simultaneously the direct unipolar leads and contiguous bipolar leads on the surface of the toad's heart, and found that the chief deflection of the contiguous bipolar lead is within the duration of the intrinsicoid deflection of the unipolar lead and not necessarily at a specific point at the onset or the end of it.

BERNSTEIN

Spang, K.: Concealed Atrioventricular Conduction. Cardiologia **23:** 116 (Fasc. 2/3), 1953.

Electrocardiograms are presented revealing the phenomenon of concealed A-V conduction (a term introduced by R. Langendorf). The basis of the concept is the fact that apparently blocked auricular impulses may actually penetrate to a certain extent into the A-V junction—without activating the ventricles—and thus exert an influence on subsequent conduction of auricular impulses, or formation of nodal impulses. This principle can be applied to the analysis of a variety of simple and complex arrhythmias. The following examples are presented with illustrative diagrams: alternation of ventricular cycle length (bigeminy) as a result of alternation of F-R intervals in a case of auricular flutter with persistent 2:1 A-V conduction; unexpected prolongation of the nodal interval in A-V dissociation due to premature discharge of the nodal pacemaker by incompletely conducted sinus impulses; apparent prolongation of the nodal interval in a case of reciprocal beating due to blockage of re-entrant impulses below the nodal pacemaker and above the ventricles.

PICK

Holzmann, M.: Unusual Findings in the Electrocardiogram in a Case of A-V Block and Alternating Bundle Branch Block. Cardiologia **23:** 116 (Fasc. 2/3), 1953.

The author describes electrocardiograms revealing variable degrees of A-V block associated with variable bundle-branch block patterns in a 28 year old man with Adam-Stokes attacks. Usually right bundle-branch block occurred with a more prolonged P-R interval than did left bundle-branch block. This is interpreted by the author from the assumption of conduction delay in both bundle branches; this delay being permanent and more marked in the left, and variable in the right bundle branch. Occasionally this bilateral intraventricular conduction defect was associated with second degree A-V block with Wenckebach periods resulting in groups, with alternation of the two QRS-T contours and of long and short P-R intervals. At other occasions, the second transmitted beat after a dropped beat had a shorter P-R than the first, or A-V conduction appeared to be enhanced in spite of an increase of the sinus rate. To explain the latter two variations of this unusual case the author invokes the presence of a supernormal phase of A-V conduction.

PICK

Haring, O. M., and Luisada, A. A.: Studies with Intravenous Gitalin. II. Ballistocardiographic and Electrokymographic Observations. Am. Heart J. **46:** 276 (Aug.), 1953.

The changes in cardiac dynamics after intravenous administration of various glycosides were studied by electrokymography in 11 persons, by ballistocardiography in 14 and by both methods in 5 persons. The subjects included normal persons, and patients with rheumatic or coronary heart disease, occasionally with hypertension. The doses and the glycosides used were as follows: gitalin, 2.5 to 4 mg.; strophanthin K, 0.25 mg.; lanatoside C, 0.40 mg.; and digitoxin, 0.20 mg. All clinical patients presented evidence of congestive failure.

Correlation of the changes in amplitude of left ventricular electrokymography with those of the heart rate revealed early decrease in one out of three normal persons and in five out of eight clinical patients. On the other hand, one hour after injection, there was an increase in two out of eight clinical patients while a decrease was still present in three out of eight. No significant change was found in normal persons one hour after injection.

Correlation of the changes of the ballistocardiographic complex IJK with those of the heart rate showed early decrease in two out of three normal persons, and in 8 out of 11 clinical patients. One hour after injection, a relative decrease was found in three out of three normal persons, and in seven out of eleven clinical patients. Three out of 11 clinical patients presented a relative increase.

The early decreased amplitude of pulsations of the left ventricle took place in a greater percentage of clinic patients than of normal persons. This decrease can be explained by the result of a reduced venous return to the heart and points to a similarity of early action of digitalis glycosides in normal persons and in patients in failure. On the other hand, one hour after the injection, one-fourth of the clinic patients presented an increase of the electrokymographic and ballistocardiographic waves. This can be explained by direct stimulation of the myocardium and was not present in normal persons.

No significant difference was found between the various cardiac glycosides in either the peripheral or the myocardial effect. This indicates that:

(1) Gitalin has a similar effect to that of other glycosides of the digitalis group; (2) clinical differences found by other workers and by the authors between the therapeutic ratio of gitalin and that of other glycosides are not due to basic difference in the mechanism of action.

RINZLER

Lepeschkin, E., and Surawicz, B.: The Duration of the Q–U Interval and its Components in Electrocardiograms of Normal Persons. Am. Heart J. **46:** 9 (July), 1953.

The purpose of this study was to establish the influence of age, sex, body weight and heart rate on the Q–T and Q–U intervals. Synchronous standard limit and precordial leads as well as the heart sounds were registered at rest in 50 normal men and 50 normal women. The following intervals were measured: the intervals from the beginning of the QRS

complex to the end of this complex (QRS), to the origin of the T wave (Q–oT), to the apex of the T wave (Q–aT), to the end of the T wave (Q–T), to the "halfway point of T" (Q–T/2), to the apex of the U wave, (Q–aU), and to the end of the U wave (Q–U). The relation of the beginning of the second heart sound to the apex and end of T and to the apex of U was also studied.

The QRS duration, when measured from the earliest to the latest points in synchronous leads, is greater than when measured in separate limb leads. It increases slightly with a decreasing heart rate but shows the greatest relation to the body size. Men have a greater QRS duration than women, but in the same height groups the values were equal for both sexes.

The Q–T duration increases with decreasing heart rate; at all heart rates women had on the average a 7 per cent longer Q–T duration than men. The components of the Q–T (Q–oT) showed the same dependence on heart rate as the entire Q–T interval.

The interval from the end of T to the apex of U was practically independent of the heart rate and sex; it averaged 0.10 second. The electrocardiogram of women is characterized not only by a longer duration of Q–T and its components Q–oT and Q–aT but also by a longer and more horizontal RS–T segment than that of men. The point when the T wave reaches one-half of its final amplitude is situated nearer to the apex of T in women than in men. These characteristics make it possible, in most normal cases, to distinguish the electrocardiogram of a woman from that of a man.

RINZLER

Rubin, I. L., Margolies, M. P., Smelin, A., and Rose, O. A.: The Ventricular Esophageal Electrocardiogram in the Diagnosis of Myocardial Infarction. Am. Heart J. **46:** 38 (July), 1953.

A comparative study was performed of the esophageal leads at ventricular levels with the standard and aV_F leads in the diagnosis of posterior myocardial infarction in a series of 100 patients, with Q waves in lead III and/or abnormal T waves in lead III and aV_F. In 12 per cent of the patients with posterior myocardial infarctions, the esophageal leads did not demonstrate the lesion while in 7 per cent, the esophageal leads were the only ones which demonstrated abnormal Q waves, which were not present in aV_F. A Q wave in the esophageal leads at ventricular levels which is greater than 25 per cent of the corresponding R wave probably indicates posterior myocardial infarction. The significance of this finding is enhanced if the Q wave is 4 mm. or more in amplitude, 0.04 second or more in duration, and if it is followed by a negative T wave. Lead aV was more consistent than the esophageal lead in the indication of the presence of posterior myocardial infarction. However, some cases showed false positive Q waves in lead aV_F. Lead aV_F was more consistent than standard lead III in the indication of posterior myocardial infarction. No false-positive esophageal leads were found in normal patients.

RINZLER

Boeckh, E. M., and Schaefer, H.: Further Investigations Concerning Electrocardiographic Vectors Determined from Chest Leads. Cardiologia **23:** 191 (Fasc. 4), 1953.

The possibility of constructing vectors from precordial leads was reinvestigated. By employing a sufficiently large number of leads arranged circumferentially on the chest, it could be demonstrated that vectors can be determined whose inclination and magnitude are hardly influenced by variations in the location of the assumed point zero, and which remain unchanged when the number of electrodes is varied. Even when sources of error, particularly those of oversimplication of conditions actually present, are taken into consideration, vectors constructed from precordial leads have, according to the authors, a definite meaning and are not affected by variations of experimental conditions. They reflect, as far as QRS vectors are concerned, the course of ventricular activation which can be interpreted in terms of electrophysical laws.

PICK

Henderson, C. B.: Ballistocardiograms after Cigarette Smoking in Health and in Coronary Heart Disease. Brit. Heart J. **15:** 278 (July), 1953.

An analysis was made of the 744 ballistocardiographic tracings derived from 124 individuals before and at intervals after smoking a cigarette. No significant changes were found in 50 normal individuals between 20 and 40 years. Of 30 normals between 40 and 60 years, 8 showed respiratory changes, 4 of whom also had changes not related to respiration. Of 40 with coronary artery disease, 15 or 38 per cent developed significant abnormalities. Two with hypercholesterolemia, one with Buerger's disease and one with diabetes all developed significant changes. Most individuals with significant changes inhaled while smoking.

These findings suggest that cardiac sensitivity to nicotine is readily detected by the ballistocardiogram and is found more frequently in cardiac patients than in normal individuals.

SOLOFF

Whipple, G. H.: Techniques for Facilitating the Quantitative Analysis of Spatial Vectorcardiograms. Am. Heart J. **45:** 823 (June), 1953.

The isoelectric point of the vectorcardiogram can be located exactly by the use of screen coordinates. A sheet of appropriately scratched plastic is placed in front of an oscilloscope screen. There will be sufficient reflection to produce luminous coordinates. The isoelectric point dot may then be centered

behind the luminous dot of the coordinate markings on the sheet of plastic by appropriate adjustments of the vertical and horizontal centering controls of the oscilloscope. The vectorcardiogram is thereby brought into a constant frame of reference wherein linear extensions of the vertical and horizontal markings will always intersect at the isoelectric point in the finished photographic print. The necessary quantitative vectorcardiographic measurements can be made on the protractor and calibrated grid-pattern which is described. These measurements lend themselves readily to simple trigonometric and geometric analysis.

RINZLER

Morton, D. R., Klassen, K. P., Jacoby, J. J., and Curtis, G. M.: The Effect of Intrathoracic Vagal Stimulation on the Electrocardiographic Tracing in Man. Surg., Gynec. & Obst. **96:** 724 (June), 1953.

This study was based upon the electrocardiographic findings in 30 patients who were found to have an inoperable bronchogenic carcinoma at the time of exploratory thoracotomy. As a palliative measure, the homolateral vagus nerve was transected just below the origin of the recurrent laryngeal nerve. In the first group studies, electrocardiograms were obtained at various stages of vagus nerve manipulation, ranging from traction of the nerve to actual transection of the nerve. Since this procedure produced no clinical or electrocardiographic effects of vagal origin, electric stimulation of the vagus nerve was performed in the second group consisting of 12 patients. Only two patients gave evidence of cardiac changes due to vagal stimulation. This consisted of prolongation of the P-R and R-R intervals, a decrease in the amplitude or inversion of the P-wave, disappearance of the P-wave, auricular tachycardia, sinus tachycardia, and suppression of the sino-auricular nodes with beats arising from varying ectopic foci. The authors concluded that cardiac changes secondary to vagal stimulation in patients under satisfactory anesthesia were less common than has been previously supposed. They further concluded that anoxia is probably the most important factor in the pathogenesis of cardiac irregularities and arrest.

DENNISON

ENDOCRINE EFFECTS ON CIRCULATION

de Grandpré, R., and Raab, W.: Interrelated Hormonal Factors in Cardiac Hypertrophy, Experiments in Nonhypertensive Hypophysectomized Rats. Circulation Research **1:** 345 (July), 1953.

Experiments were carried out on hypophysectomized rats injected with various combinations of hormones in an effort to determine their effects on the heart muscle mass. Marked cardiac hypertrophy was elicited by the administration of pituitary growth hormone (somatotrophic hormone, STH) in the absence of arterial hypertension. Thyroxine, desoxycorticosterone acetate (DCA) and cortisone appear to have ancillary and more complicated roles. Increased mechanical work of the myocardium, although an important contributory factor, was not found to be a necessary prerequisite for the development of STH-induced cardiac hypertrophy. Application of these findings to the understanding of certain clinical situations ("idiopathic" cardiac hypertrophy, acromegaly, hypertensive heart disease) is discussed.

MAXWELL

HYPERTENSION

Klayman, M. I., Silberg, N. R., and Karlen, W. S.: Death Associated with Hexamethonium and 1-Hydrazinophthalazine (Apresoline) Therapy. New England J. Med. **248:** 1109 (June 25), 1953.

The authors reported a case of a hypertensive female patient who died while on large doses of hexamethonium and 1-hydrazinophthalazine (Apresoline). For two days before admission to the hospital the patient had no bowel movements. While in the hospital she experienced severe abdominal pain and then went into shock which did not respond to therapy.

Histologic examination of the small bowel revealed edematous submucosa, with infiltration by polymorphonuclear leukocytes. No narrowing or occlusions were noted in the major mesenteric vessels. The final diagnosis was paralytic ileus of the small intestine.

It was believed that the cause of death could be explained on the basis of hexamethonium toxicity. The fact that the patient had no bowel movements for several days may have contributed to the clinical picture, since this would favor increased absorption of the drug.

It was concluded that cathartics or enemas should be instituted when a patient under hexamethonium therapy has had no bowel movement for 24 hours.

ABRAMSON

Hall, O., Hall, C. E., and Ogden, E.: Cardiac Hypertrophy in Experimental Hypertension and its Regression Following Reestablishment of Normal Blood Pressure. Amer. J. Physiol. **174:** 175 (July), 1953.

Hypertension was produced by constricting the left renal artery or by implantation by desoxycorticosterone acetate pellets. Cardiac hypertrophy resulted which completely or partly disappeared when hypertension was abolished and a period of normal blood pressure ensued. A rapid decline in blood pressure permitted the greatest amount of regression of the hypertrophy.

OPPENHEIMER

Mi[illegible]s, L. C., and Moyer, J. H.: The Acute Effects of Hexamethonium on Renal Hemodynamics in Normotensive and Hypertensive Human Subjects. Am. J. M. Sc. **226:** 1 (July), 1953.

Hexamethonium bromide or chloride was administered intravenously to 12 normotensive control patients and to 19 hypertensive patients to evaluate the effect of this agent upon renal function and hemodynamics. Renal plasma flow (RPF) and glomerular filtration rate (GFR) were measured before and after the injection of 5 to 75 mg. of the hypotensive agent. A significant reduction of blood pressure was observed in both groups although in some patients with severe hypertension only a minimal fall was recorded. In about one-half of the subjects, including both controls and hypertensives, there was either no change or an increase in renal vascular resistance with reduced glomerular filtration rate and renal plasma flow noted at the point of the maximum hypotensive effect. However, at the end of one hour, renal function had apparently improved despite maintained hypotensive effect. The second response observed in the remaining patients was a significant decrease in renal vascular resistance during the hypotensive interval so that glomerular filtration rate and renal plasma flow rates were maintained near control levels despite a reduction of blood pressure. At the end of one hour, the effects of hexamethonium were similar to those found after surgical sympathectomy. Catheterization of the renal vein during hexamethonium administration disclosed an initial reduction of oxygen consumption which increased thereafter despite maintained hypotension.

The data indicate that the acute effects of hexamethonium depend upon the degrees of renal sympathetic vasoconstriction, organic renal disease, completeness of ganglionic blockade and amount of hypotension developed. Hypertensive patients without renal disease manifest the best results with reduced blood pressure and renal vascular resistance while glomerular filtration rate and renal plasma flow are maintained. With serious organic disease of the kidneys, the use of this agent may be hazardous; frequent evaluation of renal function is imperative by means of blood urea nitrogen measurement. One should be satisfied with moderate reduction of the blood pressure in these patients rather than attempt to achieve a normotensive status.

SHUMAN

Moyer, J. H., Miller, S. I., and Ford, R. V.: Orally Administered Hexamethonium Chloride in Hypertension. J. A. M. A. **152:** 1121 (July 18), 1953.

One common denominator in the development of hypertension appears to be sympathetic predominance over the vasoconstrictor mechanisms responsible for maintaining arterial blood pressure. The paper discusses the results obtained with orally administered hexamethonium in the treatment of 120 outpatients who were followed from 3 to 18 months after instituting therapy. The conditions of this study closely parallel the conditions met in a general office practice, and the results obtained should closely parallel those obtainable in general office practice where strict supervision of the entire problem for each patient is maintained. It was apparent there can be no set dose, and the drug must be titrated to each patient to establish a proper schedule. All but 17 of the 120 patients treated responded with significant reduction in blood pressure. The amount of drug required was only slightly greater in patients with diastolic blood pressures above 140 mm. Hg. than in those with diastolic pressures less than 120 but more than 100 mm Hg. No difference could be detected between patients who responded and those who failed to respond, except that patients with severe hypertension complicated by cardiac failure and renal disease seemed to be especially resistant to therapy. The outstanding problems in therapy were those related to decreased intestinal peristalsis and periodic variability of the hypotensive response. Of the patients treated for one year or more, 64 per cent are well controlled with hexamethonium as the only therapeutic agent.

KITCHELL

Perera, G. A.: Depressor Effects of Potassium-Deficient Diets in Hypertensive Man. J. Clin. Investigation **32:** 633 (July), 1953.

Four patients with hypertensive vascular disease received desoxycorticosterone acetate subcutaneously (5 mg. doses once daily) and salt-poor diets containing about 4 Gm. of sodium chloride a day. Without alteration in fluids, calories, or sodium, potassium was restricted by the almost complete elimination of fruit juice, potato, milk and eggs, a reduction in meat and coffee, and the selection of certain fruits, cereals, and vegetables. Fats, sugars, and ginger ale were given in addition. On this regimen the protein intake was reduced from about 70 to 80 Gm. during the control period, to somewhere between 31 and 48 Gm. a day on the dietary regimen. The fat consumption was increased. Under the conditions of this experiment, restriction of dietary potassium was followed rapidly by a small but statistically significant decrease in "resting" blood pressure. Associated with the restriction of potassium, there was retention of sodium. This phenomena takes place despite the rather marked sodium retention.

The mechanism of the hypotensive action is obscure. It is probably unrelated to serum volume changes. It could not be accounted for by the decrease in protein intake, and it is doubtful if the depressor effects can be related to a loss of potassium from the heart muscle with a resultant fall in cardiac output, although this possibility cannot be

completely excluded. The author states that this study fails to exclude the possible participation of the adrenal cortex, but the results are compatible with the possibility of a direct role of cations upon neuromuscular transmission or upon blood vessel walls during the hypertensive state.

WAIFE

Hafkenschiel, J. H., and Friedland, C. K.: The Effects of 1-Hydrazinophthalazine on Cerebral Blood Flow, Vascular Resistance, Oxygen Uptake and Jugular Oxygen Tension in Hypertensive Subjects. J. Clin. Investigation **32**: 655 (July), 1953.

The effects of 1-hydrazinophthalazine (Apresoline) on cardiohemodynamics were studied in seven patients with essential hypertension. The high cerebrovascular resistance was reduced. Cerebral blood flow, oxygen uptake, and venous oxygen tension were unchanged. After a comparison of certain placebo studies in six different patients with hypertension, it was concluded that the reduction in cerebrovascular resistance after "Apresoline" is sufficient to allow the blood flow and oxygen consumption to remain constant and was comparable to that observed during the hypotensive effects induced by dihydroergocornine and protoveratrine.

WAIFE

Stewart, I. McD. G.: Headache and Hypertension. Lancet **1**: 1261 (June 27), 1953.

Mainly on the basis of a demonstration of the high incidence of headache in a large group of patients who knew about their hypertension as compared with a similarly severe group in which hypertension was not known, the author concludes that most headache in hypertension is caused by anxiety. The fallacy in using this symptom for appraisal of results of therapy is emphasized.

MCKUSICK

ReMine, W. R., Estes, J. E., Dockerty, M. B., and Priestly, J. T.: Hemiplegia Resulting from Pheochromocytoma. J. A. M. A. **152**: 808 (June 27), 1953.

Refinements in laboratory diagnosis and in the management of patients with hypertension resulting from a chromaffin tumor of the suprarenal gland have progressed significantly recently. The case reported is an example of a malignant pheochromocytoma which produced hypertension with marked fluctuation in the blood pressure. The patient was admitted to the hospital with a right hemiplegia. Removal of the primary tumor and a secondary metastatic lesion resulted in clinical improvement which to date has persisted for more than two years. In their comments the authors state that since this patient was treated, they have had additional experience with similar patients and have improved their program of control of blood pressure before, during and after operation. This is done by inserting a needle into the vein and connecting this with a three-way stopcock which then is connected to (1) a syringe of Regitine, (2) a syringe containing Arterenol, and (3) a jar of 5 per cent solution of dextrose-isotonic sodium chloride solution. If blood pressure rises significantly Regitine may be administered to neutralize circulating epinephrine and lower the blood pressure to the desired level. If the blood pressure falls after removal of the tumor Arterenol may be administered. Dextrose or sodium chloride solution infusion is to keep the needle patent during the time when neither of the other drugs is being used. During the critical period in the management of patients with pheochromocytoma (which occurs in the first 24–48 hours after operation) the continuous administration of Arterenol is advised. The rate of infusion is regulated according to the quantity of Arterenol necessary to maintain normal blood pressure.

KITCHELL

PATHOLOGIC PHYSIOLOGY

Kuo, P. T., and Schnabel, T. G., Jr.: Certain Abnormal Circulatory Dynamics of Mitral Stenosis Associated with a Major Degree of Regurgitation. Am. J. Med. **15**: 50 (July), 1953.

In studying the circulatory dynamics of patients with mitral stenosis with and without a major degree of mitral regurgitation by means of electrokymographic and ballistocardiographic technics, the authors identified a large early systolic headward ballistic wave in the ballistocardiogram of patients with a significant degree of mitral regurgitation. In two of these patients a deep V-shaped ballistic wave was also observed in early diastole. Clinical observations and various physiologic studies indicate that the forces exerted by the backflow of blood through the incompetent mitral valves are probably responsible for the production of this headward early systolic wave. Electrokymograms of the inflow tract of the left ventricle of patients with mitral stenosis and significant mitral regurgitation show a rapid lateral movement of the left ventricular wall reaching its peak in early diastole. A similar electrokymographic study of patients with only mitral stenosis shows a slow lateral movement of the left ventricular wall, reaching its peak just before the onset of the subsequent ventricular systole. Ballistocardiographic and electrokymographic studies may prove to be useful in the study of patients with mitral stenosis in whom a major degree of mitral regurgitation is suspected.

HARRIS

Kata, K.: Studies on the Velocity of the Blood Stream in the Retinal Capillaries. Keijo J. Med. **1**: 251 (Dec.), 1952.

A new apparatus was devised for measurement of the velocity of blood in the retinal capillaries.

The velocity of the capillary blood stream in the human retina when sitting quietly was about 0.77 mm. per second. After moderate exercise, it increased about 0.25 mm. per second, but 30 minutes later it returned to the velocity at repose. The velocity of the blood stream in the retinal capillaries is altered markedly by the postural changes of standing or crouching. Immediately after standing up there is slowing of the blood stream in the retinal capillaries. After 6 to 11 seconds, the stream shows marked pulsation and then in 16 to 40 seconds, it recovers its normal velocity.

The mechanism of this phenomenon may be explained as follows: the systemic blood pressure shows within about 40 seconds after standing up a certain variation from the squatting position; this initial variation of the systemic blood pressure is transmitted to the retinal capillaries; first there is an initial drop and then a secondary elevation of the capillary blood pressure. The retinal capillaries are constantly under the influence of intraocular tension, therefore, when the blood pressure of the capillaries drops considerably, the flow of the stream becomes slowed and when the pressure is raised, it becomes rapid again.

BERNSTEIN

Fowler, N. O., Westcott, R. N., and Scott, R. C.: Normal Pressure in the Right Heart and Pulmonary Artery. Am. Heart J. **46:** 264 (Aug.), 1953.

A study of pressures in the right side of the heart and pulmonary artery of 18 normal subjects studied by the authors and a review of the findings of other authors in a total of 54 additional subjects indicated the following range limits of normal pressure in mm. Hg: (1) right atrial mean pressure: −2 to +5; (2) right ventricle: systole, 17 to 31.5; end diastole, −0.5 to +7; (3) pulmonary artery: systole, 11 to 29; diastole, 4 to 13; mean, 8 to 19; and (4) pulmonary capillary: mean, 5 to 13.

RINZLER

Brecher, G. A.: Venous Return During Intermittent Positive-Negative Pressure Respiration Studied with a New Catheter Flowmeter. Am. J. Physiol. **174:** 299 (August), 1953.

Application of intermittent positive-negative pressure respiration increases venous return in the vena cava above that existing during intermittent positive-atmospheric pressure respiration.

OPPENHEIMER

Brauer, R. W., Leong, G. F., and Pessotti, R. L.: Vasomotor Activity in the Isolated Perfused Rat Liver. Am. J. Physiol. **174:** 304 (Aug.), 1953.

At equal portal pressures blood flow in the isolated liver is five times that of the liver in the intact animal. The isolated liver is responsive to vasoconstrictor agents. The isolated liver destroys a vasoconstrictor factor in fresh heparinized blood. This hepatic vasoconstrictor material is nondialyzable and is released into the circulation for at least 90 minutes in the nephrectomized, eviscerated and adrenalectomized rat. It is suggested that the kidneys inactivate it since there is less activity in the circulation when they are present. The hepatic vasoconstrictor material is not epinephrine, histamine, pitressin or serotonin. It is not an immunologic reaction.

OPPENHEIMER

Little, R. C., Strain, Jr., S. F., and Schaefer, R. D.: Effect of Initial Length on the Work of the Cardiac Atrium. Proc. Soc. Exper. Biol. & Med., **83:** 258 (June), 1953.

Strips of left atrial muscle from the dog heart were subjected to varying degrees of stretch and the work performed during contraction was calculated. Maximum work occurred at approximately 30 per cent stretch. The average filling volume of the dog is 3.4 cc. If it is assumed that the atria are spherical this gives a surface of 10.93 sq. cm. To increase this surface by 30 per cent, it is necessary to increase the volume to 5.03 cc. Employing volume elasticity curves of the left atrium, the maximum left atrial systolic work occurs at an intra-atrial pressure of 150 mm. of water.

MINTZ

Edwards, C. C., and Reinecke, R. M.: Effect of Ischemia of the Tail of the Mouse on the Subsequent Local Blood Pressure. Am. J. Physiol. **174:** 289 (Aug.), 1953.

The authors observed a reduction in local blood pressure in the tail of the mouse after 8 to 12 hours with the tail in a pneumatic sheath at 150 mm. Hg pressure. The reduction was found some distance proximal to the area at which pressure was applied. It was not part of a generalized low peripheral blood pressure.

OPPENHEIMER

Lavenne, F., Tyberghein, J., and Sonnet, J.: The Action of Procaine Amide in the Syndrome of Wolff-Parkinson-White. Acta Cardiol. **8:** 834 (Fasc. 4), 1953.

In two out of four cases of Wolff-Parkinson-White syndrome administration of 1 to 2 Gm. Pronestyl orally, or 500 mg. intravenously, led to temporary disappearance of the anomaly. The action of the drug is discussed with reference to the mechanisms supposedly involved in the production of the syndrome. In the two cases with positive response (disappearance of anomalous conduction) the author believes that Pronestyl diminished the irritability of a hyperexcitable ventricular focus which, during the time of the anomaly, was stimulated by each auricular action and thus produced the pre-excitation syndrome. In cases which do not respond with

normalization of A-V and intraventricular conduction another mechanism, namely an accessory A-V conduction pathway could be postulated. Thus, according to the author, administration of Pronestyl in a case of Wolff-Parkinson-White syndrome permits the differentiation of the two possibly underlying mechanisms.

PICK

Fowler, N. O. Jr.: Further Studies of the Relationship Between Pulmonary Arteriolar Resistance and Pulmonary Artery Pressures. Am. Heart J. **46:** 1 (July), 1953.

This study is of the relationship between pulmonary artery, mean, systolic, and diastolic pressures on the one hand, and pulmonary arteriolar resistance on the other. It was carried out in 39 human beings, some normal and others having a variety of heart and lung diseases. There was a high degree of association found between pulmonary arteriolar resistance and the other measured pressures. In the patients studied, pulmonary resistance could be estimated from any of these pressures from regression equations, but not with precision, since there is considerable scatter about the regression line. The data suggest that the diastolic pressure is a less reliable guide to the pulmonary vascular resistance than is either the mean or systolic pressure, but there is not a significant difference in the accuracy of any of the three pressures as a guide to pulmonary vascular resistance.

RINZLER

Berger, A. J., and Rackliffe, R. L.: Treatment of Paroxysmal Supraventricular Tachycardia with Methoxamine. J. A. M. A. **152:** 1132 (July 18), 1953.

Methoxamine hydrochloride (Vasoxyl) successfully ended attacks of supraventricular tachycardia complicated by vascular collapse in two patients. One patient received a 20 mg. dose intravenously and another received a 10 mg. dose intramuscularly. The drug acted rapidly (in one case 15 minutes, in the other 30) by restoring normal rhythm. It does not cause cardiac irritability and may prove to be the drug of choice in the treatment of supraventricular tachycardia.

KITCHELL

Stephenson, H. E., Jr., Reid, C. and Hinton, J. W.: Some Common Denominators in 1200 Cases of Cardiac Arrest. Ann. Surg. **137:** 731 (May), 1953.

It is postulated that the absolute frequency of cardiac arrest is actually increasing, and therefore it is quite right that efforts be redoubled toward an increasing understanding of this problem. An analysis of the reasons behind this increase in cardiac arrest suggests the following possible explanations: the widespread use of a multiplicity of drugs and combined anesthetic agents during a single operative procedure; the expanding field of thoracic and cardiac surgery; an improved definition of cardiac arrest as well as sharper indications for cardiac massage; and finally, the almost universal use of the endotracheal tube, increased frequency of bronchoscopies, esophagoscopies, cardiac catheterizations, angiograms, etc. Twelve hundred cases collected from this country and various other countries of the world are carefully analyzed as to the significant factors involved. It is significant that 14 per cent of cases occurred outside the operating room and therefore a hospital plan of action must be set up to meet this emergency. The time factor is most important in successful resuscitation. Ninety-four per cent of all successful cases were massaged within the first four minutes, whereas only 6 per cent were successful if massage were started after four minutes. Cardiac arrest in this series was more common in the male and more cases occurred in the first decade of life. The authors emphasized the importance of the vagovagal reflex as a mechanism in the causation of cardiac arrest. Anoxia and hypoxia potentiate this reflex. The thoracic approach to cardiac massage is preferred. In this series a permanent survival rate of 28 per cent was reported and the heart beat was restarted in 56 per cent of all cases.

DENNISON

Melrose, D. G.: Mechanical Heart-Lung for Use in Man. Brit. M. J. **2:** 57 (July 11), 1953. **Melrose, D. G., Bassett, J. W., Beaconsfield, P., Graber, I. G., and Shackman, R.: Experimental Physiology of a Heart-lung Machine in Parallel with Normal Circulation.** *Ibid.*, p. 62. Editorial: The Artificial Heart. *Ibid.*, p. 86.

The design of the machine is based on that of the pump-oxygenator described by Björk and Crafoord. The blood spreads over annular perspex plates so arranged to provide a maximum surface area of blood exposed to oxygen. Two valveless rotary type pumps are used, one (the venous pump) to supply the oxygenator with blood, and the second (the arterial pump) to deliver oxygenated blood to the subject. Harmonious operation of the two pumps is regulated automatically by signals from manometers measuring volume of blood in the oxygenator and pressures in the two segments of the artificial circulation. A range of flow from 300 to 3000 cc. is possible. Adjustment of rate of oxygen delivery is possible and acid-base balance is maintained by changes in the oxygen flow rate and by addition of small amounts of carbon dioxide. Sterilization is accomplished chemically although autoclaving is thought to be possible soon as a result of some alterations.

Results of the use of the machine in parallel with the normal circulation of 30 anesthetized dogs is described. Blood was fed to the machine from the

femoral vein and returned to the femoral artery. At a perfusion rate of 750 to 1000 cc. per minute as much as 150 cc. of oxygen could be introduced into the circulation per minute. Fifty per cent reduction of leukocytes, mainly granulocytes, occurred, but recovery occurred in two hours after the end of the procedure. Platelets and erythrocytes fell to a lesser extent. A slight rise in plasma hemoglobin indicated hemolysis.

The editorial writer suggests that this method might be useful not only in cardiac surgery but also in treatment of acute, potentially reversible anoxia such as that which accompanies acute cor pulmonale or myocardial infarction. Hazards and unsolved problems are presented in review.

McKusick

PATHOLOGY

Daniel, R. A. Jr., and Scott, H. W. Jr.: Aortic Stenosis: A Surgical Problem. Ann. Surg. **137:** 745 (May), 1953.

The historical background, pathologic physiology and clinical manifestations of aortic stenosis are thoroughly discussed. The profound problems and technical considerations involved in any surgical attack on the stenotic aortic valve are presented including the various operative approaches previously developed. The authors present three cases of aortic stenosis operated on through the transventricular approach. Two of the patients were operated on through a basal transventricular approach using digital palpation of the valve, dilatation of the valve and also the use of the dilating instrument. One patient was operated on through the apical transventricular approach but digital palpation is impossible and only the dilating instrument was used. It is felt that the transventricular approach to the aortic valve is the most satisfactory. Whether to make the incision at the base of the ventricle or at the apex may depend on the age of the patient, and the character of the myocardium. The authors suspect that since a patient with aortic stenosis may very quickly and shortly become markedly disabled because of a slight increase in the increment of obstruction at the valve that perhaps patients may be vastly benefited by a moderate or even a slight increase in the size of the valve opening.

Dennison

Conklin, G. J., and Mantz, F. A. Jr.: Isolated Myocarditis in Infants. J. Pediat. **42:** 414 (April), 1953.

Two cases of isolated (Fiedler's) myocarditis in infants are recorded. A clinical diagnosis was established in one case on the basis of bradycardia, low-grade fever, syncope, and changing electrocardiograms for which no other apparent cause could be discovered. Although the fever altered by penicillin, no therapeutic responses were elicited by sulfadiazine or atropine in high dosage, and these agents failed to prevent syncope and death.

The pathology and etiology of isolated myocarditis are discussed briefly. It is postulated that isolated myocarditis is a chronic progressive disease ending in granulomatous inflammation in patients who survive long periods. Isolated myocarditis should be considered in the differential diagnosis of cryptogenic cardiac arrythmias and cardiac enlargement occurring in infants.

Bernstein

Webster, B., Rich, C., Jr., Densen, P. M., More, J. E., Nicol, C. S., and Padget, P.: Studies in Cardiovascular Syphilis. The Natural History of Syphilitic Aortic Insufficiency. Am. Heart J. **46:** 117 (July), 1953.

The authors present an investigation of the course of 1,020 patients with the clinical diagnosis of syphilitic aortic insufficiency followed in the Johns Hopkins Hospital and the New York Hospital over a period of 20 years; three-quarters of these patients were followed throughout the study period or until the time of death. The following definite conclusions were reached: (1) After an initial high risk of hospitalization, there is a steady incidence of hospitalization which does not change through the years; after ten years, 10 per cent and 21 per cent of the patients at the New York and Johns Hopkins Hospitals, respectively, not admitted at the time of diagnosis had subsequently one or more hospital admissions. (2) The long time prognosis was good; 43 per cent and 33 per cent of the patients surviving 10 years and 30 per cent and 20 per cent surviving 15 years at the two hospitals. (3) Of the patients seen when less than 40 years old, 35 per cent survived 10 years, whereas 21 per cent of those over 65 years at the time of diagnosed survived this period. (4) Fifty-one per cent of patients free of symptoms at the time of diagnosis survived 10 years; the figure for such survival for diagnosis at the time of symptoms was 29 per cent. Those free of symptoms at all times had a 10 year survival of 58 per cent. Of those originally free of symptoms who later developed them, 25 per cent survived 10 years from the time of onset. (5) Of those patients free of failure at the time of diagnosis, 32 per cent survived 10 years and of those without angina at time of diagnosis, 26 per cent survived this time. The 10-year survival for those who had these two symptoms at the time of diagnosis was 6 per cent and 28 per cent, respectively. (6) Of the patients who died, 75 per cent died with predominant symptoms of cardiovascular disease. (7) Of the patients autopsied, the diagnosis of syphilitic aortic insufficiency was substantiated in 93.2 per cent of those at the New York Hospital and 84.5 per cent at the Johns Hopkins Hospital.

The following conclusions were less definite: (1) The effect of race and sex was difficult to evaluate and correlate with the type of work performed and economic factors, but women did better than men

and whites better than nonwhites. (2) The effect of work could not be investigated reliably because of technical difficulties. (3) The effect of treatment prior to or after the time of diagnosis could not be investigated reliably.

RINZLER

Kay, J. H., Thomas, V., and Blalock, A.: The Experimental Production of High Interventricular Septal Defects. Surg. Gynec. & Obst. **96:** 529 (May), 1953.

In order to study the physiologic and pathologic changes that accompany such defects, an ingenious method was devised which consisted of using an instrument similar to a sharpened cork borer. An interventricular septal defect could be produced by inserting the instrument through the right ventricular wall and exerting pressure and suction on the instrument while making a rotary motion. The instrument was advanced until it engaged the interventricular septum immediately beneath the pulmonary valves. An attempt was made to direct it so that it emerged immediately beneath the aortic valves in the left ventricular cavity, having passed through the septum at a very high point—the most frequent anatomic position of congenital interventricular septal defects. Fifty-nine per cent of the animals survived the immediate postoperative period and the defects remained patent in approximately 84 per cent of these animals. Cardiac catheterization studies performed seven or more months after production of the defect revealed a shunt of blood from left to right amounting to eight to 49 per cent of the total pulmonary blood flow. In addition, a slight to moderate right ventricular hypertension and an even smaller rise in pressure in the pulmonary artery was found. The defects were so large in some of the dogs that they died of congestive heart failure.

DENNISON

PHARMACOLOGY

Rohn, R. J., and Bond, W. H.: Some Effects of Nitrogen Mustard and Triethylene Melamine in Acute Disseminated Lupus Erythematosus. Am. J. M. Sc. **226:** 177 (Aug.), 1953.

Nitrogen mustard and triethylene melamine were employed in five patients with lupus erythematosus because of its effect in other sensitization disorders including glomerulonephritis and arthritis. In three of five patients with Lupus erythematosus remissions were obtained lasting from 6 to 217 days compared to corticotropin-induced remissions of 14 to 300 days. One patient made no response to corticotropin or the cytotoxic agents. When a response to the latter was obtained, skin lesions disappeared, fever, pain, and arthropathies were controlled; there was a definite decrease in the number of "L.E." cells in the bone marrow. Maintenance therapy has not been attempted because of a marrow hypoplasia which follows a prolonged use of these agents; however, it is suggested that concomitant corticosteroid administration may retard this effect. Evidence is presented to show that nitrogen mustard is not effective through stimulation of the pituitary-adrenal axis; a most convincing example of this was the failure of ketosteroid excretion to rise during treatment. Treatment with cytotoxic agents may be indicated in patients in whom infection, psychosis, or resistance to the corticosteroids interdicts their use. Nitrogen mustard may be useful in the acute crises of lupus or in patients with renal involvement.

SHUMAN

Lu, G., and Krantz, J. C.: Anesthesia. XXIX: The in vitro Studies of the Influence on Adenosine Triphosphate (ATP) Dephosphorylation by Central Depressants and Stimulants. Anesthesiology **14:** 348 (July), 1953.

The rate of adenosine triphosphate-dephosphorylation of rat and dog-brain homogenates was measured in vitro under the influence of a variety of central depressants and stimulants. Only the ethers, chloroform and certain alcohols had a slight depressive effect at narcotic or twice narcotic concentrations, whereas many other central depressants had no effect. The central stimulants had irregular effects. The conclusion was reached that both narcosis and stimulation in the central nervous system do not primarily involve adenosine triphosphate-dephosphorylation.

MAXWELL

Burn, J. H.: Acetylcholine and the Heart Beat. Lancet **1:** 1161 (June 13), 1953.

The inhibiting effect of acetylcholine on cardiac muscle (as opposed to its stimulating effect on skeletal muscle) and the slowing of the rate of an ectopic pacemaker by quinidine, an acetylcholine antagonist, raised questions about the basis for these seemingly anomalous actions. Although it had previously been suggested that acetylcholine plays a part in the contraction of heart muscle, the idea remained only a remote possibility until the demonstration by the author and his collaborators of circumstances under which acetylcholine stimulates, rather than inhibits, heart muscle: (1) the Paludrine-inhibited rabbit atrium could be made to beat again by the administration of acetylcholine; (2) atria allowed to "run down" after 24 to 30 hours in the bath would begin beating again when acetylcholine was added. Choline acetylase, which is responsible for acetylcholine synthesis, fell markedly in "run down" atria but was restored in the restarted atria.

Addition of acetylcholine to the bath containing beating atrium resulted in the classical inhibitory effect. In such atria choline acetylase was at least partially inhibited suggesting that the action of acetylcholine in decreasing the rate and force of the

heart beat may be in part due to depression of the synthesis of acetylcholine. Eserine, a cholinesterase inhibitor, caused an increase in the rate and force of contraction of isolated heart preparations.

The author suggests that quinidine raises the threshold to acetylcholine with the result that the time taken for acetylcholine to be formed in sufficient concentration in an ectopic focus to discharge a contraction wave is prolonged and the rate of discharge is slowed.

McKusick

Nadell, J.: The Effects of the Carbonic Anhydrase Inhibitor "6063" on Electrolytes and Acid-Base Balance in Two Normal Subjects and Two Patients with Respiratory Acidosis. J. Clin. Investigation **32:** 622 (July), 1953.

Certain heterocyclic sulfonamides are potent inhibitors of the enzyme, carbonic anhydrase. Detailed electrolyte studies in two normal subjects and two patients with pulmonary emphysema and respiratory acidosis show that a preparation "6063" caused a transient increased urinary pH and an increase in the urinary carbon dioxide, sodium, potassium, and phosphate. The urinary ammonia excretion fell. Concurrently, there was a fall in the arterial pH and carbon dioxide content. Plasma potassium concentration showed a transient decrease. Although the plasma carbon dioxide content remained depressed while the drug was administered, the daily urinary excretion of these electrolytes returned to control levels in two or three days. A rebound phenomena was prominent after the drug was discontinued. This lasted for more than a week and consisted of a decreased urinary excretion of sodium, a rise in blood pH, and other changes.

It is concluded that inhibition of carbonic anhydrase in the kidney leads to a decreased acidity of the urine due to the reduced availability of hydrogen ions from carbonic acid. The urinary excretion of sodium is increased because of a disruption of the exchange mechanisms in the renal tubules by which the hydrogen ion is normally excreted by the tubule cell and the sodium reabsorbed.

Gastric analyses performed before and during therapy with this carbonic anhydrase inhibitor revealed no significant change in the secretion of free or combined acid in the gastric juice.

Waife

Miller, A. J., Shifrin, A., Kaplan, B. M., Gold, H., Billings, A., and Katz, L. N.: Arterenol in Treatment of Shock. J. A. M. A. **152:** 1198 (July 25), 1953.

Arterenol has been used in the treatment of 40 episodes of shock from various causes in 32 patients reported. Nine patients were in shock following acute myocardial infarction. Excellent pressor responses were gotten with treatment in 25 of the 32 patients. In five patients the pressor response was moderate and in two there was no response. Such results strongly suggest arterenol to be a valuable adjuvant to the therapy of shock. There was no evidence that arterenol increased myocardial irritability and no undesirable reactions were noted. There was no instance of heart failure precipitated or aggravated by the drug, and there were no apparent ill effects in patients digitalized before or during the therapy. Various types of shock were encountered and arterenol was effective in all of them. In oligemic shock it was effective as interim therapy until whole blood could be obtained.

Kitchell

PHYSICAL SIGNS

Currens, J. H., Thompson, W. B., Rappaport, M. B., and Sprague, H. B.: Clinical and Phonocardiographic Observations on the Flint Murmur. New England J. Med. **248:** 583 (Apr. 2), 1953.

This study concerns observations made in 24 patients with aortic regurgitation, all but one due to syphilitic heart disease. Fourteen were found to have a presystolic murmur. Two of these 14 persons were studied at autopsy and found to have normal mitral valves. One of these two had aortic regurgitation resulting from a bicuspid aortic valve associated with coarctation of the aorta. Although the heart was enlarged in the majority of cases, three patients had hearts of normal size. It is felt that left ventricular dilatation is apparently not essential to the production of the Flint murmur, but may predispose the heart to such a murmur. The difficulty of distinguishing between the Flint murmur and that of mitral stenosis is mentioned. Features suggesting mitral stenosis are said to include the mitral opening snap, accentuation of the apical first heart sound and a delay in onset of the first heart sound by phonocardiogram beyond 0.08 second from the Q wave of the electrocardiogram.

Rosenbaum

Gmachl, E.: Meso- and Telesystolic Acoustic Phenomena. Ztschr. Kreislaufforsch. **42:** 502 (July), 1953.

The author studied phonocardiograms and classified various acoustic phenomena occurring in the middle and at the end of ventricular systole. Mesosystolic and telesystolic extra sounds have ordinarily no hemodynamic significance. Frequently they are due to pleuro-pericardial adhesions, but they occur in normal persons without obvious cause. Mesosystolic murmurs may likewise be caused by synechiae between pleura and pericardium, or may represent a particular form of functional systolic murmurs. The former variety is frequently characterized by a scratching "extracardiac" quality of the murmur. Murmurs occurring in the terminal

part of systole may be insignificant, but may occasionally be heard in the presence of mitral disease.

PICK

Strano, A., and Monaco, R.: Phonoarteriographic Registration of the Autochtonic Murmurs Due to Organic Arteriopathies. Cardiologia **23**: 230 (Fasc. 4), 1953.

In patients with organic lesions of peripheral arteries of various etiology arterial murmurs can be heard with maximal intensity at the site of the actual lesion. These murmurs were recorded and analyzed as to their timing and significance.

All records had in common oscillations of about 0.20 second duration, starting 0.18 to 0.20 second after the Q wave of the electrocardiogram, and coinciding precisely in time with the peripheral sphygmogram. The murmurs are unrelated to alterations of the oscillometric index, and may precede them. The authors explain the mechanism of the murmurs on the basis of loss of elasticity in the affected section of the artery, which results in local modification of tone of the vascular wall and conversion of a mechanical phenomenon into an acoustic one.

The authors emphasize the necessity of systematic auscultation of peripheral arteries in patients suspected of having a vascular disorder, since occurrence of a localized arterial murmur permits the diagnosis and localization of an anatomic arterial lesion even before the development of local clinical manifestations.

PICK

Biehl, J. P., and Simon, D. L.: Auricular Sounds in a Case of Auricular Flutter. Am. J. Med. **15**: 134 (July), 1953.

The authors report a case of complete heart block in a woman of 41 in whom the diagnosis of auricular flutter was subsequently made on the basis of rapid precordial clicks which had persisted for almost a year.

HARRIS

Boas, E. P.: The Evolution of Calcareous Aortic Stenosis. Geriatrics **8**: 142 (March), 1953.

The physical signs and symptoms of calcareous aortic stenosis are discussed in the light of their gradual evolution in 15 patients who were personally observed for from two to 20 years (on the average, 11.5 years). Long before the pathognomonic thrill appears the diagnosis may be suggested by the presence of a harsh or musical systolic murmur. This murmur may be heard all over the precordium; it may be loudest at the apex or at the aortic area. This murmur becomes more significant if it is accompanied by an aortic diastolic murmur or by the anginal syndrome. In patients in whom the murmur initially is heard loudest at the apex, the point of maximum intensity gradually shifts to the aortic area, and then a systolic thrill may become palpable in the second right interspace. In this series progress of the valvular lesion was not associated with any manifestations of recurrent rheumatic activity.

BERNSTEIN

PHYSIOLOGY

Weil-Malherbe, H., and Bone, A. D.: The Adrenergic Amines of Human Blood. Lancet **1**: 974 (May 16), 1953.

The authors describe a differential fluorimetric method for the simultaneous but separate estimation of adrenaline and noradrenaline in human plasma and red cells. Tests demonstrating the specificity and accuracy of the method are presented. The mean concentration of adrenaline in plasma was found to be 1 to 1.5 micrograms per liter of whole blood and that of noradrenaline about 5.2 micrograms per liter of whole blood. Erythrocytes contain more adrenaline and less noradrenaline than plasma. Erythrocytes of females contain more of the adrenergic amines than those of males.

MCKUSICK

Sheppard, C. W., Overman, R. R., Wilde, W. S., and Sangren, W. C.: The Disappearance of K^{42} from the Nonuniformly Mixed Circulation Pool in Dogs. Circulation Research **1**: 284 (July), 1953.

The problem of simultaneous mixing and disappearance of substances injected into the circulation is discussed theoretically and analyzed mathematically. The theory is tested in experiments with injected K^{42} in dogs.

Following the rapid jugular administration of K^{42}, the plasma levels in the carotid artery assume a rapidly declining quasi-exponential aperiodic curve with three superimposed periodic oscillations. Events upstream are repeated downstream with: (a) appropriate time delay, (b) attenuation due to the intervening loss of tracer and (c) loss of resolution owing to the dispersing action of the variable circulatory paths. For the circulation as a whole, the relation between specific activity and time has a periodic and an aperiodic component. The injected material moves initially as a wave, becomes rapidly suppressed and broadened and quickly returns on itself. The combined waves then merge into a distribution of activity such that the concentration declines everywhere by the same fraction in a given interval of time. The extrapolated zero intercept of the aperiodic portion of the arterial curve, when corrected for time delay, yields the volume of dilution of the tracer; the figure obtained was significantly lower than accepted plasma volume for dogs. With this exception, the experimental results were in satisfactory agreement with the theoretic analysis.

MAXWELL

Forster, G., and Lottenbach, K.: Oxymetric Determination of the Circulation Time. Cardiologia **23**: 181 (Fasc. 2/3), 1953.

In 30 patients without cardiovascular disease the authors found the following normal values for oximetrically determined circulation times: lung to ear, 4 to 7 seconds, with an average of 5.5 seconds; arm to ear 9 to 15 seconds, with an average of 11.5 seconds; arm to lung, (by subtraction of the above values) 4 to 9 seconds, with an average of 6.2 seconds.

Application of the method to 100 cases with various types of heart disease revealed that right heart failure with elevation of the venous pressure invariably leads to prolongation of arm-to-lung and arm-to-ear circulation times. Abnormal circulation times particularly from arm to ear may, however, occur in the absence of right heart failure owing to an increase of diastolic rest blood volume in a failing left ventricle. In congenital heart disease shortening of the arm-to-ear circulation time to about 5 seconds proves the presence of a venoarterial shunt.

The method is of value in the detection of early and nonclinically manifested heart failure. In the course of medical and surgical therapy of heart disease, repeated oxymetric determinations of the circulation time represent a simple and objective method of assessing the effect of the treatment.

PICK

Clemedson, C. J., and Pettersson, H.: Genesis of Respiratory and Circulatory Changes in Blast Injury. Am. J. Physiol. **174**: 316 (Aug.), 1953.

Blast injury was produced by a detonating high explosive. Changes in circulation and respiration were of peripheral origin. There was little or no factor of cerebral concussion. Respiration is accelerated abruptly by vagal reflexes from the damaged lungs. Fall in blood pressure and bradycardia seem to be caused by blast pressure acting externally on the carotid sinus. Prolonged effects after the beginning are due to pulmonary reflexes.

OPPENHEIMER

Bettge, S., and Feigel, G.: Alterations of the Circulation Induced by a Pneumoperitoneum. Ztschr. Kreislaufforsch. **42**: 514 (July), 1953.

In 10 persons in supine position, acute alterations of cardiodynamics caused by an artificial pneumoperitoneum were studied by the methods of Broemser and Ranke. An almost constant finding was the reduction of the cardiac output (between 18 and 56 per cent), frequently in association with increase of the peripheral vascular resistance. Heart rate and pulse wave velocity changed in a reciprocal manner. All these alterations disappeared within 30 minutes with restitution to the original values. These rapid changes suggest that the observed alterations of cardiodynamics are caused by a neurovegetative regulatory mechanism elicited by the mechanical stimulus of the pneumoperitoneum upon the abdominal autonomous nervous system.

Determination of the circulation time by injection of ether into a leg vein revealed that the reduction of cardiac output is brought about by slowing of blood flow through the lower extremities and probably also through the splanchnic area. In no case did there remain signs of permanent impairment of cardiovascular functions by an artificial pneumoperitoneum.

PICK

RHEUMATIC FEVER

Abelmann, W. H., Ellis, L. B., and Harken, D. E.: Diagnosis of Mitral Regurgitation. An Evaluation of Clinical Criteria, Fluoroscopy, Phonocardiogram, Auricular Esophagram and Electrokymogram. Am. J. Med. **15**: 5 (July), 1953.

The authors report a detailed analysis of their extensive investigation of 62 patients with rheumatic mitral stenosis without significant involvement of other valves and without clinical evidence of rheumatic activity, who underwent mitral valvuloplasty. In addition two patients with pure mitral insufficiency are discussed. The authors failed to discover any single valid criterion for the diagnosis of marked mitral regurgitation. They believe all available data must be weighed and considered according to their merits. One may be reasonably certain that no mitral regurgitation of a degree that would contraindicate valvuloplasty is present in a patient with a typical history and findings of mitral stenosis and disability of a degree indicating operation, who has an apical systolic murmur of grade 2 or less, a left auricle moderately enlarged in posterior direction only, evidence of right ventricular enlargement by x-ray or an electrocardiogram without evidence of left ventricular enlargement, and who shows definite but slight systolic posterior expansion of the left auricle by fluoroscopy, kymogram or esophagram. Definite evidence of left ventricular enlargement, either by x-ray or electrocardiogram, in the absence of aortic disease, hypertension or myocardial failure, makes one suspect moderate mitral regurgitation. If it is associated with any or several of the other presumptive signs of mitral regurgitation, such as a very loud apical systolic murmur, marked left auricular enlargement with systolic expansion, and symptoms of fatigability and weakness overshadowing dyspnea, the authors consider regurgitation marked and probably the predominant mitral lesion. Mild to moderate mitral regurgitation does not preclude benefit from mitral valvuloplasty for stenosis. The auricular esophagram did not improve clinical quantitation of mitral regurgitation. Auricular border electrokymograms and phonocardiograms were not always of diagnostic value.

HARRIS

Brock, L. L., and Siegel, A. C.: Studies on the Prevention of Rheumatic Fever: The Effect of Time of Initiation of Treatment of Streptococcal Infections on the Immune Response of the Host. J. Clin. Investigation **32**: 630 (July), 1953.

Patients with proven early group A streptococcal pharyngitis were treated by one of four methods. Eighty-six patients received treatment immediately, consisting of three injections of 600,000 units of procaine penicillin in oil with 2 per cent aluminum monostearate at three-day intervals. Eighty-nine additional patients received the same treatment, but this was delayed three days so that the initial injection was between 70 and 79 hours from the onset of symptoms. A similar group of eighty-seven subjects was treated after a five-day delay, while eighty-seven subjects received saline placebos on the first and fifth days, and no penicillin. Immunologic studies show that there was a correlation between the time of institution of penicillin therapy and the degree of suppression of antistreptolysin formation in that the earlier the treatment, the greater the suppression. When treatment was begun not later than 31 hours after the onset of symptoms, the subsequent antistreptolysin response was reduced by 60 per cent when measured at 21 days. However, therapy begun as late as five days after the onset of symptoms also produced a significant antibody suppression. These results support the belief that the antigenic challenge during acute streptococcal pharyngitis occurs gradually over a period of several days, and an appreciable portion of the total immune response may develop as a result of antigen formation after the fifth day of the disease.

WAIFE

Luisada, A. A., and Magri, G.: Early Changes of Mitral Valve Function in Rheumatic Heart Disease. Am. J. Med. **15**: 25 (July), 1953.

Using phonocardiograms and electrokymograms, the authors performed a clinical and graphic study of 53 patients with rheumatic fever in order to evaluate early myocardial or valvular disease in these persons. The phonocardiograms revealed that two types of murmurs were most common in the early stages of rheumatic fever; (1) a soft, high-pitched, apical, systolic murmur "in decrescendo" and (2) a harsher, at times musical, "diamond-shaped" pulmonic murmur. In the later stages of the disease the apical murmur was often louder while the pulmonic was often less apparent. If healing of the lesions had occurred, both murmurs were less apparent or disappeared. The electrokymogram in a high percentage of cases revealed a pattern due to transmission of intraventricular pressure to the left auricle on account of mitral regurgitation. The correlation between clinical, phonocardiographic and electrokymographic data proved that these graphic studies are of definite help not only in establishing the diagnosis but also in evaluating the severity of the regurgitation and of the cardiac murmurs. Evaluation of the part played by muscular and valvular factors in causing regurgitation was not possible after a single examination. However, repeated examinations during and after the active stage frequently permitted such evaluation.

HARRIS

ROENTGENOLOGY

Bruwer, A.: Roentgenologic Findings in Anomalous Pulmonary Venous Connection. Proc. Staff Meet., Mayo Clin. **28**: 480 (Aug.), 1953.

A crescentic, saber-shaped shadow of vascular density that runs downward, parallel to, or behind the right side of the heart, and disappears from view in the region of the right cardiophrenic angle probably represents a vein draining all or part of the blood from the right lung into the right atrium or inferior vena cava. In addition to this characteristic crescentic shadow, other features are not infrequently seen on roentgenograms. The first consists of a variable degree of shift of the heart into the right half of the thorax, sometimes to the extent that dextrocardia is suggested. This appearance is possibly in part a reflection of enlargement of the right side of the heart. In a number of cases, it is associated undoubtedly with another relatively common feature, namely the smaller volume of the right hemothorax as compared with the left.

An important implication is that, at least in right-sided partial anomalous pulmonary venous connection, the examination is not complete unless bronchoscopic and bronchographic studies have been done. It may be of doubtful value for the patient to undergo the risk of a major operation in an attempt to correct an anomalous connection from a lung that is of questionable functional value. Another feature is that the aorta is usually small or even invisible, a situation that reflects the diminished volume of blood transmitted through it. The large size of the pulmonary artery and its ramifications is frequently noted in cases of either partial or total anomalous pulmonary venous connection. Roentgenoscopically, these vessels are seen to pulsate actively. The appearance is thought to be due to recirculation through the lungs of blood that normally would enter the systemic circulation and it is similar to the findings associated with interatrial septal defects.

SIMON

Epstein, B. S.: The Roentgenographic Aspects of Thrombosis of Aneurysms of the Anterior Communicating and Anterior Cerebral Arteries. Am. J. Roentgenol. **70**: 211 (August), 1953.

The author presents a verified case where an arterial thrombus plugged an aneurysm at the junction of the anterior communicating and anterior cerebral artery as was diagnosed by cerebral angiography. The pooling of contrast medium within an aneurysmal sac of a cerebral artery usually identifies the nature of the lesion. However, when such a site is obstructed because of an arterial thrombus

added information may be derived from pneumoencephalography.

SCHWEDEL

Sandstrom, C.: Contrast Media for the Kidneys, Heart and Vessels, and their Toxicity. Acta Radiol. **39:** 281 (Fasc. 4) April, 1953.

The author discusses toxic reactions of simple or compound organic iodide solutions used for contrast visualization. While for the most part toxic side reactions such as warmth, flushing, dizziness, vomiting and fall in blood pressure are common, shock like states, laryngeal edema and deaths are rare (though one quoted observed had five fatalities in a series of 170 patients).

The author suggests calcium gluconate for laryngospasm, urticaria, angioneurotic edema and increased irritability of the central nervous system: and oxygen and intravenous ephedrine for a profound drop in blood pressure.

SCHWEDEL

SURGERY IN HEART AND VASCULAR SYSTEM

Eisaman, J. L., Caylor, H. D., Jackson, C. E., and Roe, H.: Cardiac Arrhythmias during Anesthesia. A Comparison of Cyclopropane and Pentothal-Nitrous Oxide-Ether Anesthesia. Am. J. Surg. **86:** 23 (July), 1953.

For this study, the authors have routinely made electrocardiograms on patients undergoing major surgery. Their report gives data on the incidence of cardiac arrhythmias during cyclopropane and also during pentothal-nitrous oxide-ether anesthesia and their treatment with intravenous procaine.

Statistical data are given on the incidence of arrhythmias induced during 334 major surgical cases. Under cyclopropane anesthesia, 62 per cent had some type of arrhythmia. Multiple and multifocal ventricular premature contractions were the most frequent and dangerous arrhythmias. In this group of cases, intravenous procaine for various ventricular or combined supraventricular and ventricular arrhythmias apparently benefited 93 per cent of the patients.

With the pentothal-induced nitrous oxide-ether anesthesia, 9 per cent had some type of arrhythmia. This is in sharp contrast to the 62 per cent arrhythmias in the cyclopropane group. Only eight patients of the pentothal-nitrous oxide-ether group had ventricular arrhythmias. The auricular arrhythmias were more common in this group but not worrisome. One case of cardiac arrest occurred in each group.

DENNISON

Gulfoil, P. H., and Doyle, J. T.: Traumatic Cardiac Septal Defect. J. Thoracic Surg. **25:** 510 (May), 1953.

A case report is presented of a young man who sustained injury to the chest which resulted in rupture of the cardiac septum. Examination after the accident revealed the presence of a thrill in the left third intercostal space and a loud blowing systolic murmur heard over the entire precordium. At first, signs of congestive heart failure were present, but then they disappeared. A cardiac catheterization was performed, and the oxygen studies of blood taken from the right auricle and ventricle supported the diagnosis of an interventricular septal defect. Another catheterization was done about two months later and this time the results suggested that a large atrial septal defect was also present. One year following the injury the patient was found to be in good general condition without any significant limitation of ordinary physical activity. However, since he demonstrated a large pulmonary blood flow, it was believed that such a change would ultimately lead to disabling pulmonary vascular disease.

ABRAMSON

Kanar, E. A., Schmitz, E. J., Sauvage, L. R., Nyhus, L. M., Moore, H. G., Jr., Merendino, K. A., and Harkins, H. N.: Experimental Vascular Grafts. 1. The Effects of Dicetyl Phosphate on Venous Autografts Implanted in the Thoracic Aorta of Growing Pigs: a Preliminary Report. Ann. Surg. **138:** 73 (July), 1953.

In order to prevent the undesirable tendency of venous grafts to dilate with time, the authors studied the effect of application of crystalline dicetyl phosphate to the adventitial surface of such preparations. Fresh venous autografts of the thoracic aorta were studied in 10 weaning pigs. Five were treated with dicetyl phosphate while five were used as controls.

It was found that application of dicetyl phosphate appeared to exert some restricting effect on the subsequent enlargement of the venous autografts. However, there was no prompt control of this tendency. Furthermore, in the dicetyl phosphate preparations, there was noted, a higher incidence of atheromatous or calcific degeneration then in the control preparations, as well as a greater number of late cicatricial stenosis of the graft.

ABRAMSON

Knox, W. G., and Parsons, H.: Sympathectomy in Chronic Occlusive Arterial Disease. Am. J. Surg. **85:** 642 (May), 1953.

The effect of lumbar sympathectomy was studied in 32 patients with arteriosclerosis obliterans. As preliminary measures, various diagnostic and prognostic procedures, such as plethysmography, oscillometry, arteriography, use of vasodilator drugs and paravertebral sympathetic blocks, were utilized, however, in none did the results infallibly predict the response to sympathectomy.

The operation was found to be of value in the

majority of patients with impaired arterial circulation, particularly if vasomotor activity was present. Poor results were obtained in individuals with tissue necrosis.

ABRAMSON

Wilkinson, W. R.: Arterial Embolectomy. Report of Successful Aortic, Femoral and Popliteal Embolectomies. Am. J. Surg. **85**: 648 (May), 1953.

The author presented a brief discussion of the etiology, diagnosis and treatment of arterial embolism and reported on two such cases. In one, surgical removal was performed at the bifurcation of the aorta with an excellent result. In the other, the embolus, which was at the popliteal bifurcation, was removed 24 hours after the onset of the condition—signs of return of circulation appearing 36 hours later. Despite a lumbar sympathectomy performed 12 days after embolectomy, a temporary foot drop developed. Four days after sympathectomy, a second embolus was removed from the right femoral artery with complete recovery of the right lower extremity.

ABRAMSON

Naclerio, E. A., Maynard A. de L., and Cordice, J. W. V., Jr.: Personal Experiences with Ten Consecutive Cases of Heart Wound Treated Successfully by Pericardiotomy and Cardiorrhaphy. J. Thoracic Surg. **25**: 448 (May), 1953.

The authors presented 10 cases of injuries to the heart successfully treated by pericardiotomy and cardiorrhaphy. In all instances clinical signs of acute cardiac tamponade were observed preoperatively. The blood pressure at the time of initial examination was found to be falling or absent. X-rays demonstrated a widening of the cardiac silhouette. It was the authors' opinion that when history and physical findings were suggestive of heart injury, exploratory thoracotomy was indicated. Aspiration of blood from the pericardial sac, as a specific therapeutic measure or as a preliminary to surgery, was considered to be valuable and effective in the management of cardiac tamponade in certain cases.

ABRAMSON

Nyhus, L. M., Kanar, E. A., Moore, H. G., Jr., Schmitz, E. J., Sauvage, R., and Harkins, H. N.: Experimental Vascular Grafts. III, the Dimensional Changes in Short and Long Length Fresh and Preserved Aortic Homografts Implanted into the Thoracic Aorta of Growing Pigs: a Preliminary Report. Surg., Gynec. & Obst. **97**: 81 (July), 1953.

A study was made of the dimensional changes in fresh and preserved aortic homografts of various lengths implanted into the thoracic aorta of nine growing pigs. In none were thrombosis, rupture or dilatation noted when the animals were sacrificed. All the grafts were patent.

It was found that the duration of graft preservation did not significantly alter graft growth. Although the latter phenomenon did occur in both the short and long, and fresh and preserved thoracic aortic homografts, the rate was slower than in that of the host aorta.

ABRAMSON

Schmitz, E. J., Merendino, K. A., Kiriluk, L. B., Kanar, E. A., and Harkins, H. N.: Compilation Autografts of the Subclavian Artery for Bridging Short Defects in the Thoracic Aorta: an Experimental Study with Pertinent Human Measurements. Surg., Gynec. & Obst. **97**: 11 (July), 1953.

The authors studied the problem of the practicability of using autografts of the subclavian artery for bridging defects in the thoracic aorta. Nineteen dogs were utilized in the investigation. In each the segment of subclavian artery was removed, opened longitudinally and sutured to form a tube. The aorta was then divided between Potts clamps and the graft sutured in place. Eleven of the animals died or were sacrificed during the first two weeks after graft implantation, while the remainder survived for more than five months.

On the basis of the results, it was concluded that the subclavian artery was a readily available source of autogenous arterial tissue. It could easily be compiled or rolled into a tube of adequate diameter to repair defects of short length in the thoracic aorta of the dog. During at least a period of six months the grafts did not undergo degenerative changes. This experimental work was considered to have clinical application.

ABRAMSON

Lenegre, J., and Coblentz, B.: Mitral Commissurotomy. Arch. mal. coeur **46**: 577 (July), 1953.

The indications and contraindications for mitral commissurotomy are discussed on the basis of 80 cases, 72 of which were submitted to surgery. In 53 cases (74 per cent) the results are reported as excellent, while the over-all mortality in the operated series was 8.3 per cent (six cases).

In order to assess the indication for surgical intervention the authors consider exact roentgenologic, electrocardiographic and hemodynamic studies as indispensable. At the present stage, it appears advisable to defer surgery in cases with clinically well-tolerated mitral lesions, or with an active endocardial process. On the other hand surgery is definitely indicated in cases with pronounced symptoms and congestive failure. In the presence of mitral insufficiency or other associated valvular lesions, hypertension or chronic pulmonary fibrosis surgery can be recommended if, after evaluation of the patient, mitral stenosis proves to be the dominant lesion. Auricular fibrillation, a giant left auricle, embolic phenomena, and calcification of the mitral valve may impair the results of the operation and represent, in the opinion

of the authors, relative contraindications. A long term evaluation of the operated patients is still necessary to assess the duration of favorable results and to establish final criteria for operability.

PICK

Soulie, P., Bouvrain, Y., Fortin, P., and De Vahia, J. L.: Effective and Harmful Commissurotomies. Arch. mal. coeur **46**: 625 (July), 1953.

The authors reviewed the histories of five instances of unsuccessful commissurotomy (four with fatal outcome) which occurred in a series of 70 operated cases. In all five cases aggravation of the condition became manifest within a month after the operation, in four, in the form of attacks of acute pulmonary edema. In all cases mitral regurgitation was found at surgery; it was diagnosed prior to surgery in four on the basis of a systolic murmur, expansile pulsations of the left atrium and the contour of the pulmonary capillary pressure curves. The rapid downhill course with increasing congestive failure, further dilatation of the left atrium and development of tricuspid insufficiency (in one case) suggested that commissurotomy increased the degree of mitral regurgitation. There were, however, in the entire operated material, six cases which, despite clinical and surgical evidence of mitral insufficiency, were considerably or moderately improved by the operation.

A study of the operative notes and postmortem findings in the unsuccessful cases showed that the separation of the mitral leaflets was described by the surgeon as difficult or unsatisfactory and that severe pathologic alteration of subvalvular structures were found at autopsy. The degree of these associated lesions, particularly those involving the chordae tendineae, rather than the actual size of the mitral ostium before and after surgery, appears to determine the outcome of the operation in cases where stenosis and insufficiency of the valve are associated. Alttough it is impossible to assess the extent and the degree of the subvalvular lesions before surgery, and even at the operating table, the authors think that the presence of mitral iusnffiiciency does not necessarily contraindicate commissurotomy. They recommend the rejection of surgery only in those patients in whom more than a single sign suggesting mitral regurgitation (systolic murmur, expansile atrial pulsation, left heart strain in the electrocardiogram, or typical pulmonary capillary pulsations) is present.

PICK

Beattie, E. J., Jr., Adovasio, D., Keshishian, J. M., and Blades, B.: Refrigeration in Experimental Surgery of the Aorta. Surg. Gynec. & Obst. **96**: 711 (June), 1953.

The authors report that experimental reconstruction of the thoracic aorta has shown that hindquarter paralysis may follow temporary occlusion of the thoracic aorta. Hoping that refrigeration would permit longer occlusion time without paralysis, healthy mongrel dogs were anesthetized then refrigerated until the rectal temperature had fallen to values below 30 degrees C. Following this, under aseptic precautions, the left thorax was entered and the thoracic aorta immediately distal to the left subclavian artery dissected free and occluded for varying periods of time by means of Pott's ductus clamp. After removal of the Pott's clamp, the thorax was closed in the standard surgical fashion. Thirty-five dogs served as the basis for this report. Four of 10 dogs not refrigerated developed signs of hindquarter paralysis when the thoracic aorta was occluded for 60 minutes. There was one questionable instance of a weakness of 1 hind leg in 10 dogs refrigerated while the thoracic aorta was clamped for 60 minutes. There was no instance of hindquarter paralysis when five dogs were refrigerated while the thoracic aorta was occluded for 90 minutes. Ten additional dogs died during the refrigeration experiments. Seven of these 10 dogs died from cardiac arrest or ventricular fibrillation. The authors believe that rectal temperatures below 25 C. were particularly prone to these two complications. Large doses of Nembutal were poorly tolerated by the refrigerated dog. It was concluded that refrigeration would protect the spinal cord against temporary anoxia, but safer and better method of refrigeration are needed.

DENNISON

Wexler, D. J., Bromberg, F., and Kohn, A.: Emergency Infracostal Approach for Cardiac Arrest. Am. J. Surg. **86**: 29 (July), 1953.

A new surgical approach for the management of cardiac arrest is described. This involves employing the infracostal approach and in the authors' opinion it eliminates the need for rib-spreaders or rib resection as in the thoracic approach, and the need for opening the peritoneum or diaphragm as in the transabdominal approach. The diaphragm rises anteriorly from the posterior surface of the xiphoid by two slender fleshy slips directed backward (pars sternalis) and laterally from the deep surface of the lower six costal cartilages (pars costalis). Dissecting from below upward, the diaphragm between these two muscular origins can be readily and bluntly detached from the costal arch, entering the pleural cavity anterior and superior to the plane of the diaphragm. Thus, entrance is provided to the chest through a left subcostal incision. This allows access to the heart through a natural plane of cleavage which lies posterior to the posterior rectus sheath and transversus abdominis muscle and anterior to the peritoneum, adjacent to the xiphisternal junction.

The authors present brief reports of nine cases of cardiac arrest encountered over the past four years,

together with the plan of action and method of surgery which has been developed.

DENNISON

Neptune, W. B., Bailey, C. P., and Goldberg, H.: The Surgical Correction of Atrial Septal Defects Associated with Transposition of the Pulmonary Veins. J. Thoracic Surg. **25**: 623 (June), 1953.

The case reports of two patients with atrial septal defects and anomalous drainage of the pulmonary veins of the right lung into the right atrium are presented. The authors, using a previously described surgical technique by one of them report successful operative correction of these defects in the two patients presented. The defect was repaired by suturing the redundant wall of the right atrium to the anterior edge of the atrial septal defect. The suturing could then be extended superiorly and inferiorly to the posterior extremity of the right atrial chamber. By this maneuver, an anterior atrial compartment is produced which contains the entrance of the superior and inferior vena cavas, the coronary sinus and the tricuspid valve; posteriorly, there is a separate compartment containing the entrance of the pulmonary veins of the right lung which drain by way of the aseptal defect into the left atrium. Such a diagnosis may be suspected when the right atrial blood has a higher oxygen content than either the inferior or superior vena cava. In addition, catheterization studies may reveal a venous type pressure curve and the catheter tip may also lie within a pulmonary vein.

DENNISON

Okulicz, S. J., and Marshall, V. F.: Nephrectomy and Hypertension. The Experience in One Urologic Clinic. Am. J. Surg. **86**: 45 (July), 1953.

A review of the experience in one urologic clinic with the problem of nephrectomy and hypertension has been presented. In analyzing their results the authors have required evidence of a persistently and clearly elevated blood pressure prior to operation for classification as hypertensive. Furthermore, criteria for improvement have been strict, demanding evidence that normotension throughout a two year period and symptomatic relief be indications of an excellent outcome. Using this criteria, their results indicated that only 14 per cent of the patients seemed to have benefited in regard to the hypertension and only 6 per cent were cured. In the cases showing improvement, the renal disorder was clearly unilateral and especially it was so marked as to be a good indication for nephrectomy even if hypertension had not existed.

The authors feel that better diagnostic-prognostic tests might well provide more candidates. They also are firm in their belief that a conservative policy regarding nephrectomy in this type of case is wise.

DENNISON

THROMBOEMBOLIC PHENOMENA

Anning, S. T.: Post-partum Venous Thrombosis and Leg Ulcers. Brit. M. J. **4826**: 14 (July 4), 1953.

An analysis was made of 160 patients with leg ulcers following postpartum venous thrombosis. The latter condition occurred after the first confinement in 50 per cent of cases and after the third in about 25 per cent. The incidence of this complication was much smaller following subsequent deliveries. In about 31 per cent of patients some type of obstetrical intervention had been practiced. The venous thrombosis occurred primarily in the left lower extremity. A family history of venous impairment was present in 52 per cent, a finding which was considered to be statistically significant.

It was concluded that postpartum venous thrombosis takes place more often when labor has been long and difficult and when there has been intervention, especially by intravaginal or intrauterine maneuvers. Consequently, it is more common after first confinements.

ABRAMSON

D'Alessandro, A. J.: Venous Thrombosis. The Problem and its Management. Am. J. Surg. **85**: 652 (May), 1953.

The author discussed the various procedures utilized in the treatment of venous thrombosis and attempted to analyze them on the basis of personal experience and reported studies. It was his view that heparin was preferable to other anticoagulants, such as Dicumarol and Tromexan. Vein ligation was considered to be of limited value; its indiscriminate or prophylactic use was condemned as unnecessary, and unphysiologic, the complications often aggravating the clinical picture. Lumbar sympathetic blocks appeared to deserve some recommendation for the dramatic, symptomatic relief obtained in some instances.

ABRAMSON

West, J. P., Schetlin, C. F., and Schilling, F. J.: Thrombosis of the Abdominal Aorta Treated by Thrombo-endarterectomy. Ann. Surg. **138**: 259 (Aug.), 1953.

Insidious thrombosis of the aorta is a degenerative disease which apparently begins with atheromatous deposits in the intima. The thrombotic process is apt to be most active in those parts of the aorta where there is a change in the direction of blood flow, such as occurs at the bifurcation. Since the introduction of abdominal aortography in 1929, confirmation of the diagnosis of aortic obstruction has become a more simplified matter. There are several surgical approaches to the problem of thrombosis of the abdominal aorta. The ideal treatment of a thrombosed segment of artery appears to be resection of the obliterated zone and bridging of the vascular defect by a graft. Such a procedure is now prac-

tic[illegible] if the diagnosis is made before the thrombotic pr[illegible]ess has involved large segments of the aorta and ili[illegible] arteries.

A second method of restoring continuity of the lo[illegible]er aorta and its major branches consists of re-m[illegible]al of the thrombus and diseased intima, fol-lo[illegible]ed by simple suture of the vessels.

The authors describe the second situation in a 37 ye[illegible]r old woman with evidence of arterial insuffi-ci[illegible]ency in both legs. She was found to have an incom-pl[illegible]e obstruction of the terminal aorta and right ili[illegible] artery caused by an arteriosclerotic thrombus. An aortogram confirmed the diagnosis before there wa[illegible] complete occlusion and extensive involvement of the vessels. Thus, successful thromboendarterec-tomy was accomplished without major technical dif-ficulties and with a good surgical result.

DENNISON

Gleason, D. F., and Aufderheide, A. C.: Fatal Bone Marrow Embolism Occluding the Pulmonary Arteries. Am. J. Med. **15:** 137 (July), 1953.

The authors report a case of sudden death due to massive bone marrow embolism. The marrow apparently entered the circulation consequent to inadvertent compression of tuberculous vertebrae during cystoscopy.

HARRIS

Wallach, J. B., Lukash, L., and Angrist, A. A.: Occlusive Auricular Thrombi. Am. J. Med. **15:** 77 (July), 1953.

The authors present their studies of 16 cases of ball-valve thrombi and large auricular thrombi and review some of the relevant literature. They suggest that the cause of death in these cases is a diminution of blood flowing into the left ventricle with consequently diminished left ventricular output. This may be due to three possible mechanisms: (1) obstruction of the mitral valve orifice itself by a ball-valve or mass thrombus; (2) filling of most of the left auricle by a thrombus which acts as a space-occupying tumor, producing a reduction in the amount of blood which can be present in this chamber at any one time; (3) partial or complete occlusion of some of the pulmonary veins by thrombus in the left auricle with a resultant decrease in the amount of blood entering the left auricle (usually associated with 2). Although any of these mechanisms may occur, it is postulated that the second mechanism, frequently associated with the third is the most common manner in which these thrombi attain significance.

HARRIS

Wilkins, R. W., and Stanton, J. R.: Elastic Stockings in the Prevention of Pulmonary Embolism. II. A Progress Report. New England J. Med. **248:** 1087 (June 25), 1953.

The incidence of pulmonary embolism was studied during two periods. During a control period of 10 months no stockings of any kind were used by a series of 4450 patients who were hospitalized. During a subsequent period of 12 months all patients over twenty years of age admitted to the hospital for more than twenty-four hours wore correctly-fitted, special bed-wear, knee-length stockings. There were 5467 patients in the second group. There were 21 cases of pulmonary embolism in the control series and only 12 in the treated series. Only four of these latter patients appear to represent failure of the stocking procedure since the majority of the others failed to wear the stockings.

In the current series elastic stockings were used routinely. Only 6 per cent of patients admitted did not wear the stockings. The stockings are felt to be of no value and conceivably may do harm when definite thrombophlebitis or phlebothrombosis is already present. The stockings are considered not a substitute for, but an addition to, other measures designed to prevent pulmonary embolism, including anticoagulants and venous ligation. Results with this method are felt to warrant its consideration as a routine hospital procedure.

ROSENBAUM

BOOK REVIEWS

Extrasystoles and Allied Arrhythmias. *David Scherf and Adolf Schott.* New York, Grune & Stratton, 1953. 531 pages, 213 figures, 10 tables. $15.00

The book opens with historical remarks about pulse intermittence, a chapter which provides fascinating reading. Then, the authors present in detail the electrocardiographic, physiologic, pharmacologic and clinical aspects of the extrasystolic arrhythmias. Another section is devoted to the mechanisms of fibrillation, flutter and paroxysmal tachycardia. In addition, a full description of dissociation with interference is included in the chapter on para-arrhythmias, and another chapter deals with alternans, in view of the importance of the differential diagnosis of alternans and bigeminal rhythm. Thus, except for a systematic description of the various forms of block, this monograph on extrasystoles and allied arrhythmias actually covers most aspects and forms of abnormal formation and conduction of the cardiac impulse. Historical introductions at the beginning of each chapter stand out as authoritative surveys. The presentation of the material is primarily based on the personal experience of the authors, and gives an excellent account of their experimental and clinical research in the field of cardiac arrhythmias in the past three decades. In the preface, Scherf and Schott acknowledge their indebtedness to Wenckebach and Rothberger, the Viennese pioneers and masters in the analysis of irregular heart action, whose tradition is perpetuated in the work of the authors.

Great emphasis is placed upon the distinction between ectopic beats with accurate coupling, initiated by the beat which precedes them, and those which are independent of the preceding beat and due to the activity of an automatic (parasystolic) pacemaker. The authors advocate that the term extrasystole be reserved exclusively for the former variety of ectopic beats, although they point out that, on rare occasions, transitions from one to the other type of ectopic impulse formation occur, as in instances where the same center gives rise to both premature beats and escapes, in the few reported cases of parasystole with transition to bigeminy with fixed coupling, and in cases of intermittent parasystole with fixed coupling of the first ectopic beat. In view of these observations, and considering the admittedly hypothetic state of our knowledge regarding the genesis of ectopic beats, it would hardly appear warranted to restrict the use of the term extrasystole to only one variety of ectopic impulse formation; in addition, it does not seem wise to apply to a common clinical phenomenon a term which is based on a differentiation which cannot be made clinically, and occasionally not even electrocardiographically.

A re-entry mechanism for the explanation of ectopic beats with fixed coupling is rejected by the authors, mainly because of the difficulty of such an assumption in instances of extrasystole with long coupling. Yet, it would appear that the same difficulty applies to the hypothesis of the authors, according to which the extrasystole is formed in a circumscribed focus upon arrival of the impulse of the preceding ("initiating") beat.

Aberrant ventricular conduction as a result of lengthening of the refractory period, owing to lengthening of the ventricular cycle, is discussed in the chapter on auricular extrasystoles; however, no mention is made of the same phenomenon, which is of greater clinical importance, in the presence of auricular fibrillation or flutter. Here, a failure to interpret the aberration correctly, may be responsible for the erroneous diagnosis of ventricular ectopic beats when no ectopic beats are present, or for an erroneous diagnosis of ventricular paroxysmal tachycardia, if the same phenomenon initiates a run of beats with aberrant conduction.

In the description of the individual forms of extrasystoles of A-V nodal origin, those with blocked retrograde conduction are not discussed; they are referred to later as a very rare form of extrasystoles, originating in the stem of the bundle of His. Similarly, no illustration is included of interpolated nodal extrasystoles of the same variety. It appears only logical to assume that the secondary pacemaker of the heart may frequently be responsible for such premature beats. Evidently, the authors accept such a view without hesitation when they present dissociation with interference as an interplay between the sinus node and a faster A-V node in the presence of retrograde blockage of the nodal impulses. A similar objection must be raised to the authors' diagnosis of ventricular paroxysmal tachycardia based on the identification of an independent, slower auricular rhythm; for A-V dissociation with interference, paroxysmal tachycardia of nodal origin in the presence of retrograde block, is associated with a slower independent auricular pacemaker. If, in addition, intraventricular block is present, a distinction between supraventricular and ventricular tachycardia may be impossible.

In the discussion of "return extrasystoles" the duration of the R-P interval is compared with the P-R distance, as if both represented conduction times. Yet, the authors admit that re-entry of the impulse may occur before the retrograde impulse reaches the auricles. It would appear that the

tendency to fixed coupling of the reciprocal beats should be emphasized rather than R-P to P-R relationship. The authors conclude from the inverse relationship of R-P and P-R that, at least for part of their path, the two impulses employ the same channels. Actually, the characteristic shortening of the R-P interval of the nodal beat following a reciprocal beat seems to indicate that the major part of the conduction occurs along different pathways. The rejection by the authors of the unique case 2 of Wolferth and McMillan, an example of sinus rhythm with reciprocal auricular beats, is not justified in the opinion of the reviewer, since the variations of P-R are fully explained by concealed conduction of blocked impulses, and do not indicate complete A-V block.

Figure 39 is interpreted as showing a change from first degree A-V block to complete A-V block brought about by nonconducted auricular extrasystoles. Actually, there is no evidence of any further impairment of A-V conductivity following the auricular extrasystoles; inhibition of the sinus node after the auricular premature beats is followed by nodal escapes. Such A-V dissociation should not be called A-V block. In figures 103 and 104, supernormal phase is assumed to explain the occurrence of retrograde P waves; in fact, their presence or absence is fully accounted for by the position of the sinus P waves.

The full discussion of the reported cases of parasystole, dissociation with interference and of reciprocal rhythm ("return extrasystoles") conveys the impression that these are exceptionally rare arrhythmias; actually this cannot be maintained, in spite of the relatively small number of well-documented cases in the literature.

The statement, that on routine clinical examination A-V dissociation with interference is bound to be mistaken for sinus rhythm with extrasystoles, can be questioned. Careful auscultation should reveal variations of the first heart sound, pointing to independent auricular and ventricular actions. If this phenomenon, well known in cases of complete A-V block, is present in a case without a slow ventricular rate, a diagnosis should be considered of A-V dissociation due to relative nodal tachycardia, and "premature beats," if present, should be suspected to represent "captures." The view that digitalis takes only second place in the treatment of supraventricular tachycardia—the first going to quinidine—can be challenged. Notably, if auricular flutter cannot be ruled out, the use of digitalis for the initial treatment may be considered more satisfactory.

In spite of such unavoidable disagreement with some of the views expressed by the authors, it is the opinion of the reviewer, that their monograph is destined to find a definitive place in the library of every cardiologist. The book is recommended to all who are interested in the mechanism of cardiac arrhythmias as a well documented, authoritative account on the subject of ectopic impulse formation.

RICHARD LANGENDORF

Roentgen Diagnosis of the Heart and Great Vessels. *Erich Zdansky. Translated by Linn J. Boyd.* First American Edition, new enlarged revision. New York, Grune and Stratton, 1953. 500 pages, 334 illustrations. $15.50.

This excellent treatise, presented in an orderly and comprehensive manner, covers the field of cardiovascular roentgenology unusually well. The book is divided into nine chapters, the first of which deals with the general technic of examination, including fluoroscopy, orthodiagraphy, teleroentgenology, plastic reconstruction of the heart by means of x-rays, roentgenkymography of the heart and great vessels, and angiocardiography.

The second chapter deals extensively with the normal heart, and is subdivided into 16 sections. Great detail is taken with a complete and instructive step-by-step evaluation of the normal heart in the anterior and both oblique roentgen studies. The illustrations and colored drawings are superb, and the x-ray reproductions are exceptionally good. The detailed descriptions are worth many hours of study. The authors include elaborate discussions of pulsations of the cardiovascular shadow, cardiac measurements and roentgen tests of cardiac function. No satisfactory solution to the problem of measurement of cardiac size has been presented, however, despite numerous technics and formulas, and this leaves the reader questioning which method the author would advise. Omission of studies of the heart in the lateral roentgenogram is also regrettable, as this view is frequently of great value in diagnosis. This chapter is nevertheless of outstanding excellence, and gives a fine basis for understanding of normal cardiovascular anatomy and physiology, and their relation to the roentgen image.

Chapter three is devoted to the evaluation of atrophy, hypertrophy and dilatation of single sections of the heart. This furnishes a very good description of the inflow and outflow tracts of both ventricles, as well as an accurate survey of auricular contours and their interpretation. Chamber analysis is well detailed with fine line drawings and x-ray reproductions. This chapter is indispensable for the study of pathologic changes that occur in the cardiovascular system.

The pathologic heart forms the basis of chapter four, and constitutes excellent and vivid reading. Fourteen subdivisions are made, with the greatest emphasis on acquired and congenital malformations of the heart. These two sections on acquired and congenital lesions occupy well over half of the material in this chapter, and constitute one of the best and most enjoyable sections of the book. The text reads unusually well in this chapter, and the illustrations and diagrams are of superior quality.

Chapter five discusses diseases of the pericardium, and chapter six takes up the lesser circuit in cardiovascular diseases. The aorta and its pathologic alterations comprise chapter seven, and the pulmonary artery and its pathologic alterations are described in chapter eight. Chapter nine is a brief discussion of the lobus venae azygos. A complete and well-presented bibliography and index add to the polished completeness of this work.

A detailed study of the cardiovascular system, starting with the fundamental evaluation of the normal heart, cardiac chamber analysis and a lucid description of pathologic changes makes this textbook an extremely valuable addition to the literature. Students of this subject will gain invaluable knowledge by a meticulous review of this book.

HERMAN W. OSTRUM

AMERICAN HEART ASSOCIATION, INC.

44 EAST 23RD STREET, NEW YORK 10, N. Y.

Telephone GRamercy 7-9170

AMERICAN HEART ASSOCIATION CONFERENCE AT AMA MEETING

The American Heart Association will be represented by a special program at the 103rd Annual Meeting of the American Medical Association, to be held at the Civic Auditorium in San Francisco from June 21–25. The program will consist of a four-day "Question and Answer" Conference on various aspects of cardiovascular disease, similar to the series conducted by the Association at the AMA Annual Meeting in Chicago in June, 1952. The program is being arranged by Howard B. Lewis, M.D., University of Oregon School of Medicine.

The Heart Association will also present an exhibit of Dr. J. Scott Butterworth's fluorodemonstrator, which was awarded a gold medal at last year's meeting of the American Medical Association. The exhibit features the Association's rubber heart models illustrating various disease conditions. An exhibit of other professional educational materials available from the Association is also planned.

The schedule of the "Question and Answer" Conference follows:

MONDAY, JUNE 21

Morning Session—Chairman: John J. Sampson, San Francisco

9:00–10:00 a.m.: Pain Syndromes due to Heart Disease
10:00–11:00 a.m.: Radiological Examination in the Study of Heart Disease
11:00–12:00 a.m.: The Medical Care of Chronic Rheumatic Heart Disease
12:00– 1:00 p.m.: Pulmonary Embolism: Causes, Recognition, Treatment

Afternoon Session—Chairman: Louis E. Martin, Los Angeles

1:00– 2:00 p.m.: The Diagnosis of Congenital Heart Disease
2:00– 3:00 p.m.: The Treatment of Congenital Heart Disease
3:00– 4:00 p.m.: Congestive Heart Failure in Children: Its Causes, Recognition and Treatment
4:00– 5:00 p.m.: The Prognosis and Management of Rheumatic Fever in the Young

TUESDAY, JUNE 22

Morning Session—Chairman: Travis Winsor, Los Angeles

9:00–10:00 a.m.: The Diagnosis of Peripheral Vascular Disorders
10:00–11:00 a.m.: The Treatment of Nonsyphilitic Aortic and Peripheral Vascular Disease
11:00–12:00 a.m.: Recognition and Treatment of Systemic and Pulmonary Arteriovenous Communications
12:00– 1:00 p.m.: Syphilitic Cardiovascular Disease: Modern Methods of Diagnosis and Care

Afternoon Session—Chairman: Hans H. Hecht, Salt Lake City

1:00– 2:00 p.m.: The Differential Diagnosis of Respiratory Symptoms due to Pulmonary and Cardiac Disease
2:00– 3:00 p.m.: Cor Pulmonale: Its Causes, Recognition and Treatment

3:00– 4:00 p.m.: What is New and Important in Electrocardiography
4:00– 5:00 p.m.: The Place for Ballistocardiography in the Study of Heart Disease

WEDNESDAY, JUNE 23

Morning Session—Chairman: George C. Griffith, Pasadena

9:00–10:00 a.m.: Cardiac-Surgical Conference
10:00–11:00 a.m.: The Early Diagnosis of Rheumatic Fever
11:00–12:00 a.m.: The Selection of Patients for the Definitive Treatment of Hypertension
12:00– 1:00 p.m.: The Clinical Application of Recent Research in Atherosclerosis

Afternoon Session—Chairman: Homer P. Rush, Portland

1:00– 2:00 p.m.: The Interpretation of Cardiac Murmurs
2:00– 3:00 p.m.: The Diagnosis and Treatment of Acute and Chronic Pericardial Disease
3:00– 4:00 p.m.: The Treatment of Bacterial Endocarditis
4:00– 5:00 p.m.: The Diagnosis of Cardiac Arrhythmias at the Bedside

THURSDAY, JUNE 24

Morning Session—Chairman: David A. Rytand, San Francisco

9:00–10:00 a.m.: The Natural History of Hypertensive Cardiovascular Disease
10:00–11:00 a.m.: The Treatment of Cardiac Arrhythmias
11:00–12:00 a.m.: Diagnosis and Management of Acute Myocardial Infarction
12:00– 1:00 p.m.: Mobilization and Rehabilitation of Cardiac Patients

Afternoon Session—Chairman: Francis D. Chamberlain, San Francisco

1:00– 2:00 p.m.: What is New in the Definitive Treatment of Hypertension
2:00– 3:00 p.m.: The Modern Management of Congestive Heart Failure
3:00– 4:00 p.m.: What is New in the Treatment of Angina Pectoris
4:00– 5:00 p.m.: The Surgical Treatment of Valvular Deformities

COUNCIL ON RHEUMATIC FEVER AND CONGENITAL HEART DISEASE

A special program devoted to a discussion of rheumatic fever will be presented at the Annual Meeting of the American Rheumatism Association at the St. Francis Hotel, in San Francisco, on Saturday morning, June 19. The program will be presented in conjunction with the Council on Rheumatic Fever and Congenital Heart Disease of the American Heart Association.

ANNUAL ELECTIONS

Dr. E. Cowles Andrus, Associate Professor of Medicine at Johns Hopkins University, Baltimore, was installed as President of the American Heart Association at the annual meeting of the Assembly held in Chicago in April. Dr. Andrus succeeded Dr. Robert L. King of Seattle, who has become Chairman of the Scientific Council. Dr. Andrus has been a Vice-President and a member of the Executive Committee of the Board of Directors of the Association for several years. He is Physician-in-Charge of the Adult Cardiac Clinic at Johns Hopkins University Medical School and Consultant in Cardiology, Walter Reed Army Hospital. In 1953, Dr. Andrus was appointed to serve on the National Advisory Heart Council, official advisory body for the National Heart Institute of the U.S. Public Health Service.

Dr. Irvine H. Page, Director of Research of the Cleveland Clinic Foundation, was chosen President-Elect, to serve during the 1955–56 term. Dr. Page was formerly a Vice-President of the Association. He was the prime mover behind the Association's Council for High Blood Pressure Research which was organized in Cleveland in 1947, and served as the Council's first Medical Advisory Chairman. Dr. Page has also served as President of the Cleveland Area Heart Society.

New Vice-Presidents elected at the Assembly meeting are: Dr. William H. Bunn, Chief of Medicine, Youngstown (Ohio) Hospital Association; Mrs. Douglass O. Burnham, Watertown, Conn., National Chairman of the Association's Committee on Volunteer Activities; S. DeWitt Clough, Managing Director of the Chicago Heart Association; Dr. David D. Rutstein, Professor of Preventive Medicine, Harvard University, Boston; Ben H. Wooten, President of the First National Bank in Dallas.

Vice-Presidents re-elected are: Dr. Edgar V. Allen, Mayo Clinic, Rochester, Minn.; A. W. Robertson, Pittsburgh, former Chairman of the Board of Directors of the Association; Dr. John J. Sampson, Chief of the Medical Division, Mt. Zion Hospital, San Francisco; and Dr. Robert W. Wilkins, Associate Professor of Medicine at Boston University. Berkeley D. Johnson, Vice-President of the United States Trust Co., New York, was re-elected Treasurer.

Among those elected to a new category of Board membership known as Directors-at-Large were: General Mark W. Clark, Charleston, S. C., former Commander-in-Chief in the Far East; Mrs. Alben W. Barkley, Paducah, Ky., wife of the former Vice-President of the United States; and Bruce Barton, New York advertising executive, author and former Congressman, who also continues as Chairman of the Board of Directors. Mrs. Barkley is a former Vice-President of the Association. General Clark headed the 1954 Heart Fund campaign.

Other Directors-at-Large elected by the Assembly were: Irving B. Hexter, Cleveland (two year term); Dr. Edgar Hull, New Orleans (one year term); Dr. T. Duckett Jones, New York (three year term); Dr. H. M. Marvin, New Haven (three year term); S. E. McCreless, San Antonio (one year term); Donald N. McDonnell, New York (two year term); Elfred S. Papy, Atlanta (one year term); William Woods Prince, Chicago (two year term); Howard C. Sheperd, New York (two year term); Dr. Helen B. Taussig, Baltimore (two year term); Frederick K. Trask, Jr., New York (three year term); Dr. Irving S. Wright, New York (one year term).

Board Members

New members of the Board of Directors elected for three-year terms by the Assembly from nominations of affiliated Heart Associations in various parts of the country were: Dr. William H. Block, Hartselle, Ala.; William A. Bowen, Apponaug, R. I.; Albert Cree, Rutland, Vt.; Dr. A. Wilbur Duryee, New York; Dr. Jose N. Gandara, Santurce, P. R.; Dr. George C. Griffith, Los Angeles; D. H. Griswold, Chattanooga; Mrs. James Harris, Alexandria, La.; Dr. Eric P. Hausner, Santa Fe, N. M.; George R. Jones, Chicago; Dr. R. Bruce Logue, Atlanta; George M. MacLeod, Wilmington; James Stuart, Indianapolis; Dr. Louis F. Viko, Salt Lake City; Dr. Bernard J. Walsh, Washington D. C.; J. Harold Williams, Hartford.

The following were elected to fill vacancies on the Board: Charles L. Bybee, Houston (one year term); Dr. George R. Herrman, Galveston (two year term); Richard P. Holland, Boston (two year term); George Rentschler, Cincinnati (one year term).

Board Members Representing Councils and Sections

In addition to the Assembly elections to the Board, the Association's Councils and Sections have selected the following to represent them on the Board for a one-year term:

Representing the Scientific Council as a whole: Dr. Robert L. King, Seattle; Dr. E. Sterling Nichol, Miami.

Representing the Section on Circulation: Dr. Nelson W. Barker, Rochester; Dr. George E. Burch, New Orleans.

Representing the Council for High Blood Pressure Research: Frank E. Joseph, Cleveland; Adrian D. Joyce, Cleveland.

Representing the Section on Clinical Cardiology: Dr. Emmet B. Bay, Chicago; Dr. William G. Leaman, Philadelphia.

Representing the Section on Cardiovascular Surgery: Dr. John H. Gibbon, Jr., Philadelphia; Dr. Robert E. Gross, Boston.

Representing the Section on Basic Science: Dr. William F. Hamilton, Augusta; Dr. Hymen S. Mayerson, New Orleans.

Representing the Council on Community Service and Education: Dr. William A. Brumfield, Jr., Syracuse; Dr. Martin Cherkasky, New York.

Representing the Council on Rheumatic Fever and Congenital Heart Disease: Dr. J. G. Fred Hiss, Syracuse; Dr. George M. Wheatley, New York.

SECOND WORLD CONGRESS OF CARDIOLOGY AND 27TH SCIENTIFIC SESSIONS OF AMERICAN HEART ASSOCIATION

All those planning to attend the Congress, scheduled to convene in Washington, D. C., September 12 through 17, are urged to *submit their applications at the earliest possible date to facilitate arrangements for groups participating in the scientific tours and social functions.* Because these groups will be limited in number, everyone who registers for the Congress will receive a special Form C, on which they may indicate their choice of the medical sightseeing tours of scientific significance, in addition to the social functions, such as the banquet and receptions. Detailed information concerning the Congress is available from the Secretary-General, L. W. Gorham, M.D., Second World Congress of Cardiology, % American Heart Association at 44 East 23rd Street, New York 10.

Medical Tours

A highlight of the Congress program will be a series of medical sightseeing tours to institutions of scientific interest. On Wednesday afternoon, September 15, participants may attend lectures, demonstrations and exhibits dealing with various aspects of cardiology which are planned at the George Washington University Hospital; Georgetown University Medical Center; Howard University Medical School; Children's Hospital; U. S. Veterans Administration, Mt. Alto Hospital; Walter Reed Army Medical Center; Army Medical Service Graduate School; Research Laboratories of the Army Medical Service Graduate School; Armed Forces Institute of Pathology; and the National Naval Medical Center. The schedule will also include a Clinical Pathological Conference in the Main Auditorium of the National Guard Armory, and a discussion of programs, grants, research, fellowships and traineeships by James Watt, M.D., Director of the National Heart Institute, at the National Heart Institute of the U. S. Public Health Service.

A sightseeing program on Friday afternoon, September 17, will include conducted tours of the Armed Forces Institute of Pathology and its Medical Museum; Armed Forces Medical Library; and the National Heart Institute. Dr. Watt's discussion at the National Heart Institute will be repeated.

Membership

A registration fee of $25.00 has been established for the combined World Congress and Scientific Sessions. Although it has been customary in previous years to waive registration fees for professional members of the American Heart Association attending the Annual Scientific Sessions, the heavy expenses entailed by the enlarged and integrated sessions of the forthcoming Congress and the many events associated with an international meeting of this kind require that a fee be charged this year. The $25.00 fee entitles members to attend all scientific sessions, the opening reception, formal banquet and other social events planned for Congress delegates, the exhibits and special sightseeing tours to medical installations in Washington and its environs. Also included are the printed program, directory of registrants, Congressional badge and other items.

Associate membership (wives and family) has been arranged at a cost of $15.00. It will include all privileges mentioned above except the printed program. *A schedule of reduced fees has been provided for limited attendance by physicians and for attendance by such groups as medical students, interns, and nurses.*

Exhibits

Scientific and industrial exhibits have been planned for the Congress, as well as a motion picture program of professional and scientific films on cardiovascular subjects. Those wishing to present scientific exhibits or films should communicate with Charles D. Marple, M.D., Medical Director of the Association. Industrial firms interested in presenting an exhibit should communicate with the Exhibit Manager, Steven K. Herlitz, 280 Madison Avenue, New York 16.

Schedule

A tentative schedule of the Congress follows:

Saturday, Sept. 11, 5:00 to 10:00 p.m.: Registration, Mayflower Hotel

Sunday, Sept. 12:
9:00 a.m. to 10:00 p.m.: Registration, Mayflower Hotel
10:30 a.m.: Opening ceremonies at Constitution Hall
5:00 p.m.: Reception for Congress Members, Pan American Building
Monday, Sept. 13 through Friday, Sept. 17: Scientific Sessions at National Guard Armory.
Morning sessions will be held every day from 9:00 a.m. to 12:30 p.m.
Afternoon sessions will be held every day except Wednesday, Sept. 15 and Friday, Sept. 17, from 2:00 p.m. to 5:30 p.m. Sessions will be composed of round table and clinical pathological conferences (panel discussions) in a large auditorium and presentation of scientific papers in four smaller section rooms.
Monday, Sept. 13, 8:30 to 10:30 p.m.: Visit to National Gallery of Art, for Congress Members only.
Tuesday, Sept. 14, 8:00 p.m.: Formal banquet for Congress Members, to be held simultaneously at Mayflower and Statler Hotels.
Wednesday, Sept. 15, 2:30 p.m.: Medical sightseeing tours to institutions of scientific interest.
Thursday, Sept. 16, 8:30 p.m.: Special entertainment for Congress Members.
Friday, Sept. 17, 2:30 p.m.: Medical sightseeing tours.

SECTION ON CIRCULATION

The Section on Circulation of the Scientific Council is planning a special scientific session for members on matters of peripheral circulation as well as a general session to be held in connection with the Second World Congress of Cardiology in Washington, D. C., September 12–17. The exact dates of this Section's meeting will be announced later.

The Executive Committee of the Section on Circulation will meet on Monday evening, September 13. The Annual Dinner of the Section will be held on Wednesday evening, September 15, at the Shoreham Hotel. Additional details may be obtained from the Secretary, Grace M. Roth, Ph.D., Mayo Clinic, Rochester, Minn.

COUNCIL FOR HIGH BLOOD PRESSURE RESEARCH

The Annual Meeting of the Association's Council for High Blood Pressure Research will be held in the fall of this year instead of the spring as has been the custom. *The meeting has been scheduled for Friday and Saturday, October 22 and 23, in Cleveland.* The subject of the scientific program will be the metabolism of muscles and nerves as it relates to high blood pressure. Irving S. Wright, M.D., New York, Past President of the Association, is Chairman of the Program Committee. A program for the general public will feature a discussion on problems of retirement.

PROCEEDINGS

The Proceedings of the 1953 Annual Meeting of the Council for High Blood Pressure Research have been published as a cloth-bound, 96-page hard cover monograph which is available from the American Heart Association or Affiliated Heart Associations at $2.00 a copy. The book includes five reviews of recent original investigative work presented at the 1953 Annual Meeting of the Council held in Cleveland last May. It compiles in one convenient reference volume material which otherwise is scattered throughout medical literature.

The authors are Doctors R. W. Sevey, Georges M. C. Masson, Simon Rodbard, D. M. Green and George A. Perera. The subjects covered include the relations between hypertension and the anterior pituitary, the adrenal cortex, renin, salt-water balance, sodium metabolism and electrolyte metabolism.

The 1953 Proceedings is the second volume in a projected series. The first volume, the Proceedings of the 1952 meeting, is still available at a cost of $1.75, paperbound.

GOLD HEART AWARDS

The Association's Gold Heart Award, given annually for outstanding contributions to the advancement of cardiovascular medicine and the Heart Program, was presented this year to Howard B. Sprague, M.D., Clinical Associate in Medicine, Harvard Medical School, and S. DeWitt Clough, Managing Director of the Chicago Heart Association, at the Annual Dinner in Chicago in April.

Dr. Sprague was cited for his profound influence on "the growth and development of the American Heart Association through his distinguished services in its highest councils and during his presidency in 1950–51." Dr. Sprague

also was President of the New England Heart Association from 1941 to 1947. He served as Secretary of the American Heart Association from 1937–1947. Since 1925, Dr. Sprague has been Senior Associate Physician in the Cardiac Clinics of the Massachusetts General Hospital. He is also Area Consultant in Cardiology, Area 3 U. S. Veterans Administration and Senior Consultant in Medicine, U. S. Naval Hospital.

Mr. Clough, honored for his outstanding activities on behalf of the Heart Program, has been on the Board and the Executive Committee of the Association since 1952. He is Honorary Chairman and Consultant of the Abbott Laboratories in Chicago and a Director of the University of Chicago Cancer Foundation.

DR. KING RECEIVES MEDALLION

The Association's Distinguished Service Silver Medallion was presented to Robert L. King, M.D., as retiring President, at the Annual Dinner. Dr. King is Chief of Medical Service of the Virginia Mason Hospital in Seattle, Clinical Associate Professor of Medicine at the University of Washington School of Medicine and Consultant in Cardiology to the Department of Health, Territory of Alaska.

DR. ALBERT SZENT-GYÖRGYI RECEIVES 1954 ALBERT LASKER AWARD

Albert Szent-Györgyi, M.D., director of the Institute for Muscle Research, Woods Hole, Mass., has received the 1954 Albert Lasker Award of the American Heart Association for distinguished achievement in the field of cardiovascular disease. The Award, conferred annually by the Albert and Mary Lasker Foundation through the Association, was presented by Irving S. Wright, M.D., Past President of the Association, at the special scientific program of the Section on Clinical Cardiology held in conjunction with the Thirtieth Annual Meeting of the Association in Chicago. Dr. Szent-Györgyi received a prize of $1,000, a scroll describing his accomplishments, and a gold statuette of the Winged Victory of Samothrace, symbolizing victory over death and disease.

The citation accompanying the award lauded Dr. Szent-Györgyi as "an extraordinarily creative explorer of the frontiers of human knowledge." The citation stated that in the course of investigations of muscular contraction, Dr. Szent-Györgyi and his co-workers discovered actomyosin, the essential contractile element of muscle. It declared that Dr. Szent-Györgyi and his associates had thereby "opened new areas of cardiac research and provided new insight into the fundamental physiology of the heart's action. Through Dr. Szent-Györgyi's pioneering work, new clues have been found to the mechanism of heart failure, and many barriers to the study of the normal and diseased heart muscle have been removed."

The internationally known biochemist, who is a research investigator of the American Heart Association, won the 1937 Nobel Prize in Medicine for the isolation of vitamin C. Dr. Szent-Györgyi also discovered vitamin P. His study of muscular contraction, begun in 1939, was interrupted by World War II and resumed on Dr. Szent-Györgyi's arrival in the United States from Hungary in 1949. In addition to the Nobel Prize, he has been honored for his achievements in the fields of biologic oxidations, muscular contraction and vitamins.

AMERICAN SOCIETY FOR THE STUDY OF ARTERIOSCLEROSIS

Abstracts of papers for presentation at the Annual Meeting of the American Society for the Study of Arteriosclerosis must be submitted to the Program Chairman by May 31. The meeting will be held at the Sheraton Hotel in Chicago on October 31 through November 1, 1954. Program Chairman is Arthur C. Corcoran, M.D., Cleveland Clinic, Cleveland, Ohio.

UNIVERSITY OF PENNSYLVANIA COURSE

The Graduate School of Medicine of the University of Pennsylvania announces the inauguration of an eight-month full-time basic course in cardiology to begin on Sept. 28, 1954. This course, which will be given under the direction of William D. Stroud, M.D., will cover the fundamentals of cardiovascular medicine, and has been planned to provide a foundation for residency and other clinical

training leading to qualifications for the practice of cardiology as a specialty. Inquiries should be addressed to the Dean, Graduate School of Medicine, 238 Medical Laboratories Building, University of Pennsylvania, Philadelphia 4, Pa.

PROGRAM OF SECTION OF CLINICAL CARDIOLOGY

The printed program of the scientific meetings of the American Heart Association's Section on Clinical Cardiology held in Chicago last April 3–4 is available from the Association at 50 cents a copy. The program contains abstracts of the papers presented and those read by title only. Copies may be obtained by writing to the Medical Director, Charles D. Marple, M.D.

MEETINGS

May 21–23: Fourth Annual Postgraduate Seminar, Mt. Sinai Hospital of Greater Miami; Sherman R. Kaplan, M.D., Mt. Sinai Hospital, 4300 Alton Rd., Miami Beach 40, Fla.

June 14–18: Canadian Medical Association; Vancouver, B. C. T. C. Routley, M.D., General Secretary, 244 St. George St., Toronto 5, Ont.

June 18–19: American Rheumatism Association; San Francisco; W. H. Kammerer, Secretary, 33 East 61st Street, New York 21.

June 19: International Society of Angiology, North American Chapter; Hotel Mark Hopkins, San Francisco, Calif. Dr. Henry Haimovici, Secretary, 105 East 90th Street, New York.

June 20: Society for Vascular Surgery; San Francisco; George D. Lilly, Secretary, 25 S.E. Second Avenue, Miami 32, Fla.

June 21–25: American Medical Association, Annual Meeting; San Francisco; Dr. George F. Lull, Secretary, 535 North Dearborn Street, Chicago 10, Ill.

July: South American Congress of Angiology; São Paulo, Brazil; Dr. Rubens Carlos Mayall, Rua Senador Vergueiro 73, Rio de Janeiro, Brazil.

July 9–10: European Society of Cardiovascular Surgery; Edinburgh, Scotland; A. J. Slessor, Department of Surgery, University New Building, Edinburgh 8, Scotland.

July 12–22: International Gerontological Congress; London and Oxford, England; Professor R. E. Tunbridge, President, General Infirmary, Department of Medicine, The University, Leeds, England.

July 20–24: International Conference on Thrombosis and Embolism; Basle, Switzerland; W. Merz, M.D., Honorary Secretary, Chief Medical Officer, Gynecological Clinic, University of Basle, Basle.

Aug. 9–13: National Medical Association; Washington, D. C. John T. Givens, Secretary, 1108 Church Street, Norfolk 10, Va.

Sept. 6: American Society of Clinical Pathologists; Washington, D. C. C. G. Culbertson, Secretary, 1040 W. Michigan Street, Indianapolis 6, Ind.

Sept. 6–10: International Congress of Clinical Pathology; Washington, D. C. Robert A. Moore, M.D., Chairman, Committee on Arrangements, Washington University School of Medicine, St. Louis 10, Mo.

Sept. 9–10: Vermont Heart Association and University of Vermont College of Medicine Seminar on Cardiac Arrhythmias; Burlington, Vt., E. Lepeschkin, M.D., University of Vermont College of Medicine, Burlington, Vt.

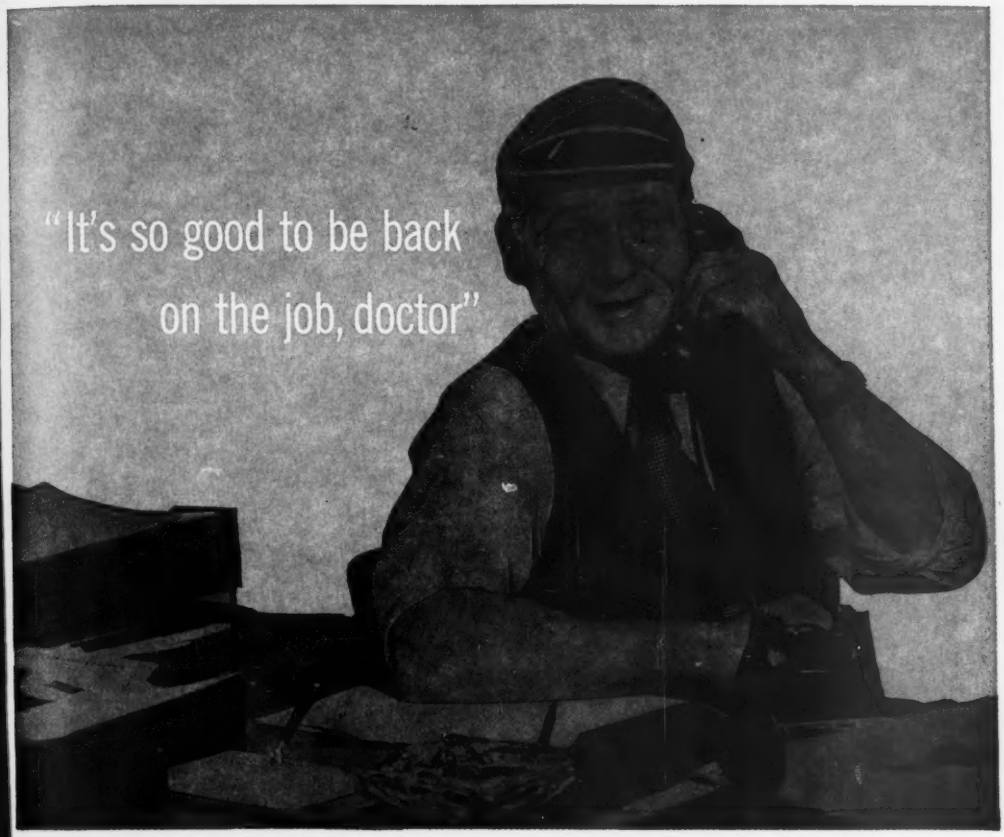
Sept. 11: Vermont Heart Association and University of Vermont College of Medicine Symposium on U wave of the Electrocardiogram; Burlington, Vt., E. Lepeschkin, M.D., University of Vermont College of Medicine, Burlington, Vt.

Sept. 12–17: Second World Congress of Cardiology and the 27th Annual Scientific Sessions of the American Heart Association; Washington, D. C. L. W. Gorham, M.D., Secretary-General, c/o the American Heart Association, 44 East 23rd Street, New York 10.

Sept. 26–Oct. 2: World Medical Association, Rome, Italy. Louis H. Bauer, Secretary, 345 East 46th Street, New York 17, N. Y.

Oct. 4–8: International Congress on Diseases of the Chest; Barcelona, Spain. Murray Kornfeld, Executive Secretary, 112 East Chestnut Street, Chicago 11, Ill.

Oct. 17–20: Association of American Medical Colleges; French Lick, Ind. Dean F. Smiley, Secretary, 185 North Wabash Avenue, Chicago, Ill.

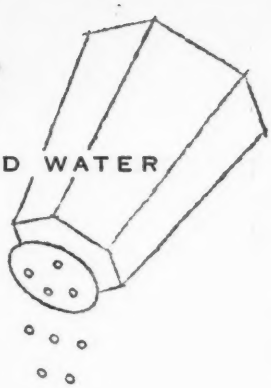


TABLET

NEOHYDRIN®

BRAND OF CHLORMERODRIN

NORMAL OUTPUT OF SODIUM AND WATER



PRESCRIBE NEOHYDRIN whenever there is retention of sodium and water except in acute nephritis and intractable oliguric states. You can balance the output of salt and water against a more physiologic intake by individualizing dosage. From one to six tablets a day, as needed.

PRESCRIBE NEOHYDRIN in bottles of 50 tablets.
There are 18.3 mg. of 3-chloromercuri-2-methoxy-propylurea in each tablet.

Leadership in diuretic research
Lakeside LABORATORIES, INC., MILWAUKEE 1, WISCONSIN

Circulation

A JOURNAL of the AMERICAN HEART ASSOCIATION

MAY 1954
VOL. IX NO. 5

CONTENTS

INTRINSIC BLOOD PRESSURE.....*Robert M. Anderson* 641

STUDIES MADE BY SIMULATING SYSTOLE AT NECROPSY. IV. ON THE RELATION BETWEEN PULSE PRESSURE AND CARDIAC STROKE VOLUME, LEADING TO A CLINICAL METHOD OF ESTIMATING CARDIAC OUTPUT FROM BLOOD PRESSURE AND AGE.....*Isaac Starr, T. G. Schnabel, Jr., S. I. Askovitz, and A. Schild* 648

CLINICAL TESTS OF THE SIMPLE METHOD OF ESTIMATING CARDIAC STROKE VOLUME FROM BLOOD PRESSURE AND AGE.....*Isaac Starr* 664

ANTICOAGULANT THERAPY IN PRIVATE PRACTICE.....*Charles A. L. Stephens, Jr.* 682

STUDIES ON THE RENAL CIRCULATION AND RENAL FUNCTION IN MITRAL VALVULAR DISEASE. I. EFFECT OF EXERCISE.....*Lars Werkö, Edvardas Varnauskas, Harald Eliasch, Jan Ek, Härje Bucht, Bengt Thomasson, and Jonas Bergström.* 687

STUDIES ON THE RENAL CIRCULATION AND RENAL FUNCTION IN MITRAL VALVULAR DISEASE. II. EFFECT OF APRESOLINE....*Lars Werkö, Edvardas Varnauskas, Jan Ek, Härje Bucht, Bengt Thomasson, Jonas Bergström, and Harald Eliasch.* 700

VENTRICULAR FUNCTION. I. STARLING'S LAW OF THE HEART STUDIED BY MEANS OF SIMULTANEOUS RIGHT AND LEFT VENTRICULAR FUNCTION CURVES IN THE DOG.....*Stanley J. Sarnoff and Erik Berglund* 706

A NEW ELECTROCARDIOGRAPHIC PATTERN OBSERVED IN CEREBROVASCULAR ACCIDENTS.....*G. E. Burch, Robert Meyers, and J. A. Abildskov* 719

FRONTAL PLANE STUDIES OF HOMOGENEOUS TORSO MODELS
Ernest Frank and Calvin F. Kay 724

CLINICAL CONFERENCES

THE USE OF ANTICOAGULANT DRUGS IN AMBULATORY PATIENTS
Emmett B. Bay, Wright R. Adams, Richard J. Jones, Robert G. Page, and Morris Seide 741

LONG-TERM ANTICOAGULANT THERAPY.....*Irving S. Wright and others* 748

CLINICAL PROGRESS. MEDICAL ASPECTS OF PATIENTS UNDERGOING SURGERY FOR MITRAL STENOSIS.....*Lewis Dexter, Lawson McDonald, Murray Rabinowitz, George A. Saxton, Jr., and Florence W. Haynes* 758

ABSTRACTS..... 771

BOOK REVIEWS..... 792

AMERICAN HEART ASSOCIATION..... 794